applied for contraceptive purposes (Swerdloff et al. 1979).

II.4.6.2.2 Androgen Derivatives

Testosterone derivatives have been developed adapting the molecular structure such that the substance is taken up after oral administration and that aromatization to oestrogens is decreased. A number of publications have suggested a potential benefit of mesterolone (Schering, Berlin, Germany) (Schellen and Beek 1972; Von Mauss 1974; Barwin 1982). However, no beneficial effect on semen characteristics or on the occurrence of pregnancies was observed when the usual dose of 75 mg/day of mesterolone was given (WHO 1989). Neither was treatment with a high mesterolone dose of 150 mg/day effective in a double-blind trial that extended over a 12-month period (Gerris et al. 1991).

Testosterone-undecanoate (Andriol, Organon, The Netherlands) is a non-toxic testosterone derivative that is absorbed after oral administration (Horst et al. 1976) and increases the concentration of mainly 5-alpha-dihydrotestosterone in peripheral blood (Skakkebaek et al. 1981). Testosterone-undecanoate exerts little suppressive effect on hypothalamo–pituitary function when given in the recommended dose of 120 mg/day (Luisi et al. 1978). Because spermatogenesis and epididymal function largely depend on high local concentrations of both testosterone and dihydrotestosterone, trials were undertaken on the effect of 120 or 240 mg/day testosterone-undecanoate for the treatment of patients with idiopathic oligozoospermia. The favourable effect observed with the first dose (Pusch 1989) was not confirmed when the high dose of 240 mg/day was given (Comhaire 1990). The only positive effect on sperm characteristics was a moderate increase of the percentage of live spermatozoa, but no effect was observed on sperm concentration, proportion motility, linear velocity or sperm morphology.

II.4.6.3 Gonadotrophins

II.4.6.3.1 Urinary Gonadotrophins

Whereas treatment with human menopausal gonadotropin (hMG, a source of both FSH and LH), or with purified urinary FSH together with human chorionic gonadotrophin (hCG) is of great benefit to patients with hypogonadotrophic hypogonadism (Liu et al. 1999), its possible usefulness in men with normo-gonadotrophic idiopathic oligozoospermia has not been proven. Meta-analysis of published data indicates an average success rate of 3.8 conceptions per cycle, but most studies refer to short periods of treatment (Winters and Troen 1982).

Patients who do not present an increase of testosterone concentration during treatment with tamoxifen may benefit from gonadotrophin treatment, since it can be hypothesized that their hypothalamo pituitary function is impaired or suppressed.

II.4.6.3.2 Recombinant Gonadotrophins

The advent of recombinant pure FSH may open new avenues for gonadotrophin treatment. Indeed, pure FSH will probably not suppress the pulsatile release of LHRH and LH, maintaining the pulsatile exposure of the seminiferous tubules to highly variable and elevated testosterone concentrations. In uncontrolled trials, a satisfactory success rate of pure FSH treatment was reported in patients with idiopathic oligozoospermia (Foresta et al. 2002; Caroppo et al. 2003), but this was not confirmed in a placebo-controlled trial (Kamischke et al. 1998). Recombinant FSH treatment has also been recommended for patients with failed IVF due to poor semen quality (Acosta et al. 1992), though this approach has become obsolete since the introduction of intracytoplasmic sperm injection (ICSI).

II.4.6.4 Luteinizing Hormone Releasing Hormone (LHRH)

Pulsatile LHRH can be delivered by means of a portable computerized pump, resulting in a physiological stimulation of pituitary gonadotrophin secretion. This treatment may offer new prospects for the management of patients with hypogonadotrophic hypogonadism of hypothalamic origin. Preliminary trials of treating patients with normo- or hyper-gonadotrophic idiopathic testicular failure with pulsatile LHRH have given inconclusive or negative results (Comhaire 1992).

Nasal or subcutaneous application of high doses of LHRH agonists results in downregulation of pituitary gonadotrophin secretion and suppression of testicular function, both hormonogenesis and spermatogenesis.

II.4.6.5 Treatments Interfering with Oestradiol

Treatment may aim at interfering with the biological effect of oestradiol, either through inhibiting its synthesis by means of aromatase inhibitors, or through blocking its effect on target cells by anti-oestrogens.

II.4.6.5.1 Testolacton

Experience with testolacton, a potent aromatase inhibitor, has been moderately positive in an open study on a small number of patients (Vigersky and Glass 1981), but no significant effect was observed in controlled double-blind trials (Dony et al. 1985; Clark and Sherins 1989). Newer aromatase inhibitors (anastrozole, exemestan, letrozol) have not been tested for the treatment of idiopathic oligozoospermia.

II.4.6.5.2 Anti-oestrogens

Anti-oestrogens have largely been used in the treatment of patients with oligozoospermia. Clomiphene citrate is a racemic mixture of two isomers, and it exerts a significant intrinsic oestrogenic activity in addition to its dominant anti-oestrogenic effect (Heller et al. 1969). No beneficial effect of clomiphene citrate was evidenced for the treatment of patients with idiopathic oligozoospermia in a double-blind trial organized by World Health Organization (WHO 1992).

Tamoxifen is a specific anti-oestrogen and is devoid of intrinsic oestrogenic activity when applied at the dose of 20 mg/day in men (Comhaire 1976). This substance stimulates the hypothalamic release of LHRH by setting the threshold of feedback at a higher level. As a result, the secretion of LH, FSH and testosterone is increased by between 60% and 100% (Fig. II.4.28). A more than twofold increase of sperm concentration occurs after 4–6 months of treatment (Vermeulen and Comhaire 1978), with significant increase of sperm motility and linear velocity (Fig. II.4.29). Sperm morphology is barely influenced. In a meta-analysis of 6 studies involving 402 patients followed during a total of 2025 months, the overall success rate was 29% with a monthly conception rate of 4.6%.

The effective cumulative pregnancy rate during tamoxifen intake evidences a clear-cut increase in the 4th, 5th and 6th months of treatment, whereas no such effect seems to be present during the initial 2 months (Fig. II.4.30). This is probably related to the fact that several months of treatment is needed before the full effect on spermatogenesis occurs. Tamoxifen treatment was found to result in a stronger positive effect on pregnancy rates in cases with low pre-treatment sperm concentration (Comhaire 2000).

Adamopoulos et al. (2003) published the outcome of a prospective double-blind, placebo-controlled trial

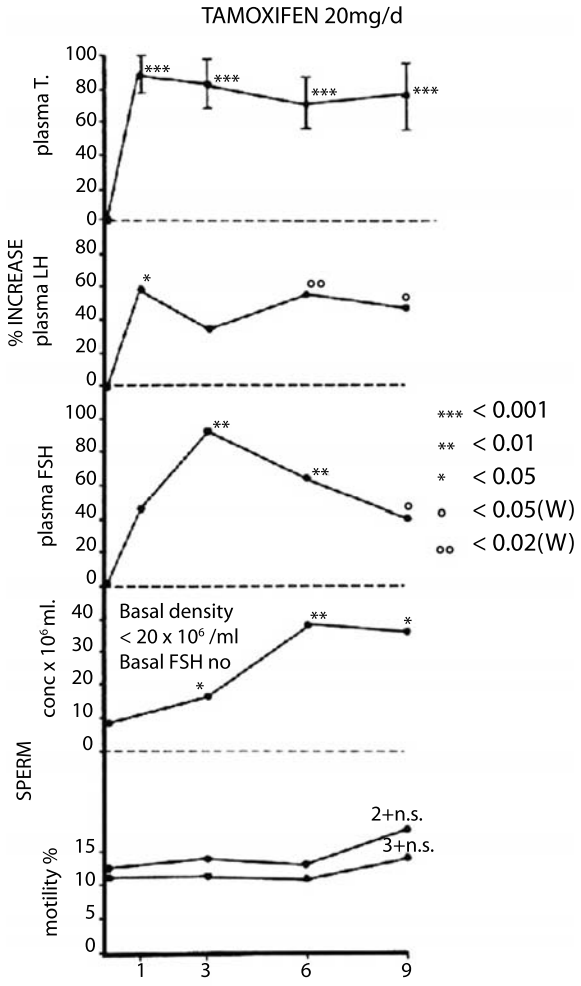

Fig. II.4.28. Effects of treatment with 20 mg per day of tamoxifen for 9 months, given to patients with idiopathic oligozoospermia, on the plasma concentrations of testosterone (ng/dl), LH and FSH (% increase over basal value), sperm concentration (million/ml) and motility [% spermatozoa with motility 2 = grade (b) motility; 3 = grade (a) motility]. (From Vermeulen and Comhaire 1978)

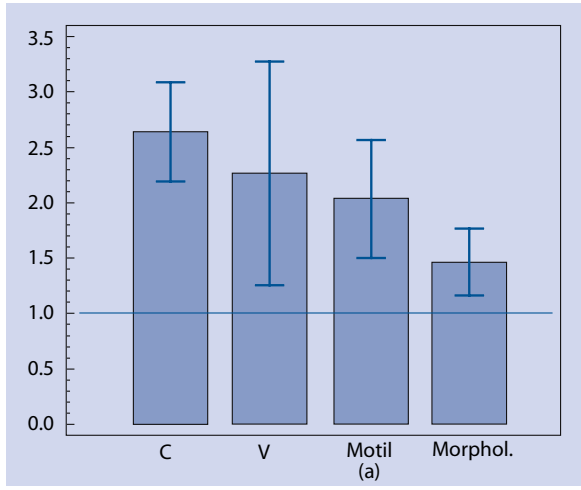

Fig. II.4.29. Ratio of sperm concentration (*C*), linear velocity (*V*), grade (a) motility [*Motil (a)*] and morphology (*Morphol.*) after 6 months of treatment with tamoxifen 20 mg per day orally divided by the values before treatment

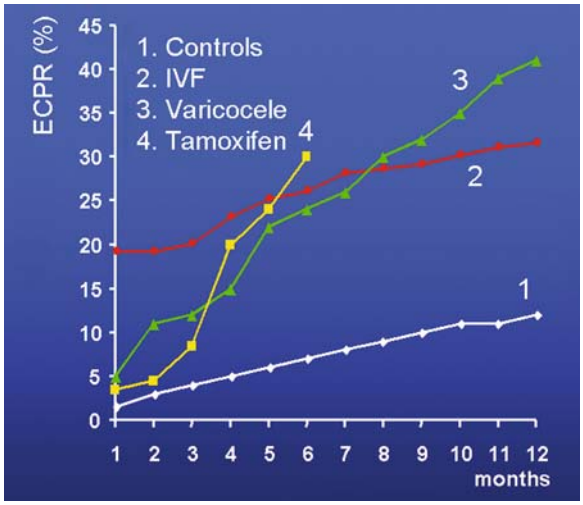

Fig. II.4.30. Effective cumulative pregnancy rate (in %, including only pregnancies resulting in successful delivery) during a follow-up period of 12 months, among couples with infertility of at least 12 months duration, no demonstrable abnormalities in the female partner, and a male factor. [*1* Controls are couples receiving counselling ("tender loving care"), *2* treatment by means of in vitro fertilization (with or without ICSI), *3* treatment of varicocele, *4* treatment with tamoxifen 20 mg/day orally)

treating patients suffering from idiopathic oligozoospermia with a combination of tamoxifen and testosterone-undecanoate. They reported a significant favourable effect of this treatment with the spontaneous pregnancy rate being 3.2 times higher in the treated cases than in the placebo controls.

II.4.6.6 Conclusion

New insights into the physiology of testicular regulation and better understanding of the pathogenesis of idiopathic male infertility hold out hope for the future possibilities of hormonal treatment. At present, the hormonal therapeutic arsenal remains limited. Antioestrogen treatment with tamoxifen is indicated, particularly in cases with low sperm concentration (ideally between 2 and 10 – 12 million/ml) and moderately disturbed sperm morphology. Tamoxifen treatment has little effect when sperm morphology is severely abnormal with less than 4% normal spermatozoa. Also, treatment with tamoxifen seems pointless in cases with elevated serum gonadotrophin levels and/or very small testicular volume.

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II.4.7 Hormonal Male Contraception

D.J. Handelsman, G.M.H. Waites

Summary

Reliable and reversible hormonal contraceptive methods for men, comparable to modern female methods, have been identified, and selected regimens are under active development through the collaboration of andrologists, public sector agencies and pharmaceutical industries.

- Clinical studies employing prototype drugs have demonstrated that the hormonal approach to switching off spermatogenesis provides contraceptive efficacy and is reversible with short-term safety.
- No regimen yet achieves consistent azoospermia in all men, although testosterone administration to men in China and Indonesia gets close.
- Combination regimens involving a second gonadotrophin-suppressing agent, usually a progestin, combined with testosterone achieve close to the ideal of universal suppression of spermatogenesis and contraceptive efficacy.

II.4.7.1 Introduction

Pituitary gonadotrophin [luteinizing hormone (LH), follicle-stimulating hormone (FSH)] secretion leading to high levels of intratesticular testosterone is essential for inducing spermatogenesis. Yet, because the hypothalamo–pituitary testicular axis is a tightly regulated negative feedback system, exogenous testosterone has the seemingly paradoxical effect of switching off spermatogenesis by suppressing pituitary gonadotrophin secretion and thereby depleting intratesticular testosterone (Handelsman 2005). Androgen-induced reversible suppression of human spermatogenesis has long been known (Heckel 1939). Extensive dose-finding and feasibility studies have established that injections of testosterone (T) esters, mostly involving weekly intramuscular injections of testosterone enanthate in an oily vehicle, induced azoospermia in most but not all men (Patanelli 1977; Schearer et al. 1978).

While these studies demonstrated that the hormonal approach was reversible and had reassuring short-term safety, the degree of sperm suppression required to provide acceptable contraceptive efficacy remained uncertain (Patanelli 1977). This issue was resolved by two large World Health Organization (WHO) clinical trials, the first male contraceptive efficacy studies, which established that azoospermia induced by weekly injections of testosterone enanthate provided highly reliable and reversible contraception (WHO 1990, 1996;

Waites 2003). More recently, a second contraceptive efficacy study using a depot androgen/progestin combination found high levels of spermatogenic suppression with all men achieving azoospermia and no pregnancies occurring among 55 couples during 35.5 person years of exposure (Turner et al. 2003).

II.4.7.2 Androgens Alone as Hormonal Contraceptives

Testosterone is potentially the ideal single contraceptive agent as it provides both gonadotrophin suppression and androgen replacement (Nieschlag et al. 2004). The WHO clinical trials involving 671 men in 10 countries established that 98% of all men had sperm suppression to <3 million/ml by 3–4 months (a similar rate to that after vasectomy) and that no pregnancies occurred when the men were azoospermic (WHO 1990, 1996). In the subgroup with residual sperm (0.1–3 million/ml) in the ejaculate, there were only four pregnancies in 49.5 person years; the contraceptive failure rate in the non-azoospermic subgroup (~8% per annum) was proportional to residual sperm concentration. Based on these results, the ideal goal is to achieve universal azoospermia, although the realistic minimal objective is to have <1 million residual sperm per millilitre to give an acceptable failure rate (Nieschlag 2002).

These WHO trials also revealed that >90% Asian men suppressed to azoospermia compared to only ~60% of Caucasian men, an unexplained population variation in testosterone-induced azoospermia (Handelsman et al. 1995). After cessation of testosterone, sperm reappeared within 3 months and returned to normal sperm output by 6 months. Discontinuations for acne, weight gain, polycythaemia or behavioural effects were few and readily reversible, as were changes in haemoglobin, testis size and plasma urea. There was no short-term evidence of liver, prostate or cardiovascular disorders (WHO 1990, 1996; Wu et al. 1996).

II.4.7.3 Pharmacokinetic Considerations

Weekly injections are clearly impractical and testosterone enanthate caused supraphysiological levels of testosterone which may have contributed to the incomplete spermatogenic suppression. Longer-acting depot preparations with more stable steady-state pharmacokinetics have therefore been developed: subdermal T pellets (Handelsman et al. 1990), T-loaded biodegradable microspheres (Amory et al. 2002), and the newer injectable preparations, T undecanoate (Gu et al. 2002) and T buciclate (Behre et al. 1995). All sustain physiological T levels for 2–6 months. Monthly injections of T undecanoate have demonstrated high contraceptive efficacy in Chinese men (Gu et al. 2002). Although synthetic androgens, including esters and a 7-methyl derivative of nandrolone, have been trialled by parenteral and oral routes, none yet offers greater efficacy or safety than testosterone itself (Kamischke and Nieschlag 2004; Handelsman 2005).

II.4.7.4 Safety

The safety of exogenous androgen administration concerns potential effects on cardiovascular and prostatic disease and idiosyncratic effects such as polycythaemia and sleep apnoea. The available short-term studies have generally revealed no safety concerns but long-term surveillance of actual disease endpoints rather than surrogate markers would be required, as it was for female hormonal contraception. The relationship between androgens and prostatic disease and any influence of exogenous androgens remains poorly understood. Prospective studies show little direct relationship between endogenous T levels and prostatic disease (Shaneyfelt et al. 2000). In situ prostate cancer is common in older men whereas rates of invasive prostate cancer vary considerably between populations despite similar blood T concentrations. Similarly, the relationship between androgens and cardiovascular disease are complex and poorly understood (Liu et al. 2003; Wu and von Eckardstein 2003) so that the risks, if any, from exogenous androgens in normal men cannot be predicted with any certainty. Idiosyncratic androgen effects such as polycythaemia and sleep apnoea are rare (<1%) and age-dependent so that the use of physiological doses of, and delivery systems for, T in a relatively young population minimize these risks. Clearly, for contraceptive purposes, it is prudent not to exceed physiological levels of androgen and to monitor long-term for cardiovascular and prostatic disease risk (Nieschlag et al. 2004; Handelsman 2005).

II.4.7.5 Combination Regimens as Hormonal Contraceptives

Second, non-androgenic, agents that suppress gonadotrophins include progestins, oestrogens and gonadotrophin-releasing hormone (GnRH) antagonists. Progestins are more affordable and numerous synthetic progestins are used in female contraception with oestrogen replacement therapy. They are potent inhibitors of gonadotrophin secretion and of endogenous T, and suppress spermatogenesis but require androgen supplementation to avoid androgen deficiency (Heller et al. 1959; Frick et al. 1981). In practice, androgen-progestin combinations achieve equally high rates of azoospermia as with androgens alone, approaching uniform suppression in all populations. This reduces the

practical importance of the population differences for contraception found with androgens alone, although it has implications for understanding population differences in hormone-dependent diseases.

II.4.7.6 Efficacy of Combination Regimens

Such combinations have shown important improvements in the efficacy of spermatogenic suppression (Bebb et al. 1996; Handelsman et al. 1996; Meriggiola et al. 1996) possibly by reducing the impact of residual T in supporting persistent spermatogenesis (Bouchard and Garcia 1987; Behre et al. 1992). Many studies with medroxyprogesterone acetate (MPA) given orally or by injection, combined with T by injection or by dermal gels, produce azoospermia (Patanelli 1977; Schearer et al. 1978). The azoospermia is nearly uniform in Indonesian men (Pangkahila 1991; WHO 1993), as it is in Caucasian men when the T is given as a depot implant (Handelsman et al. 1996).

Oral progestins, e.g. levonorgestrel (Foegh 1983; Bebb et al. 1996; Anawalt et al. 1999) and norethisterone (Guerin and Rollet 1988; Lobel et al. 1989) and cyproterone acetate (Meriggiola et al. 1996, 1998) have high efficacy when combined with T. Highly effective suppression of spermatogenesis also occurs with depot progestins, e.g. norgestrel (Gonzalo et al. 2002), etonogestrel (Anderson et al. 2002), depot injectable MPA (Handelsman et al. 1996; Turner et al. 2003) or norethisterone (Kamischke et al. 2002) when combined with T. A contraceptive efficacy study using a depot androgen/progestin combination found high levels of spermatogenic suppression, with all men achieving azoospermia and no pregnancies occurring among 55 couples during 35.5 person years of exposure (Turner et al. 2003).

Spermatogenesis recovers to normal post treatment but at a slower rate than with androgen alone, possibly due to prolonged residual depot effects (Handelsman 2005).

II.4.7.7 Gonadotrophin Blockade: GnRH Analogues

GnRH agonists or GnRH antagonists when combined with T replacement suppress gonadotrophins and spermatogenesis. GnRH superactive agonists achieve this by gradual desensitization of the GnRH receptors, a paradoxical response that takes days to weeks until the initial stimulation of gonadotrophin and T secretion abate, after which prolonged use achieves functional antagonism with lowered gonadotrophin and testosterone secretion. However, GnRH agonists remain partial agonists and these more affordable analogues rarely achieve azoospermia (Bouchard and Garcia 1987; Lunn et al. 1990; Behre et al. 1992). Pure GnRH antagonists, on the other hand, sustain immediate competitive blockade of GnRH receptors (Marshall et al. 1986) and in combination with T produce rapid, sustained and reversible spermatogenesis in men (Pavlou et al. 1991; Tom et al. 1992). Although modern GnRH antagonists retain some local irritation at the injection site, they otherwise have few side-effects and prolonged depot release formulations are under development, as are non-peptide GnRH antagonists.

II.4.7.8 Immunoneutralization as a Contraceptive Approach

Immunoneutralization of GnRH is not likely to be a safe and effective option for contraception (Handelsman 2005). However, immunological blockade of FSH action by vaccination theoretically offered the attractive possibility of inhibiting spermatogenesis by disrupting Sertoli cell function but without inhibiting endogenous T production. Although FSH was considered essential for human spermatogenesis, spermatogenesis and fertility persist in rodents (Singh et al. 1995; Kumar et al. 1997; Dierich et al. 1998) and humans (Tapanainen et al. 1997) lacking FSH bioactivity. Hence even complete FSH blockade might produce insufficient reduction in sperm output and function required for adequate contraceptive efficacy (Nieschlag 1986). In addition to the usual safety concerns of contraceptive vaccines, including autoimmune hypophysitis, orchitis or immune-complex disease, an FSH vaccine might be overcome by reflex increases in pituitary FSH secretion.

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II.4.8 Treatment of Gender Dysphoria

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Summary

Hormonal sex reassignment of transsexuals aims to reduce the hormonally induced secondary sex characteristics of the original sex and to induce the secondary sex characteristics of the new sex.

- In male-to-female transsexuals a complete reduction of androgen action favours feminizing effects of oestrogens. The risk of venous thrombosis is high with ethinyloestradiol but much lower with transdermal or oral 17β-oestradiol. Development of prolactinomas has been observed, usually with an overdose of oestrogens. Breast cancer, though infrequent, remains a risk.
- Female-to-male transsexuals receive high-dose testosterone treatment. If menstrual periods are not suppressed a progestin may be added. Side-effects are acceptable but extirpation of ovaries and internal genitalia in due course is recommended as a safeguard against malignant development.
- Transsexualism is increasingly diagnosed in juveniles. Hormonal treatment to delay pubertal development of their original sex may be an option.

Transsexualism is the condition in which a person with apparently normal somatic sexual differentiation of one gender is convinced that he or she is actually a member of the opposite gender. It is associated with an irresistible urge to be that gender hormonally, anatomically and psychosocially.

In 2004, the international organization involved with professional help to transsexuals, the Harry Benjamin International Gender Dysphoria Association, drafted Standards of Care (SOC) available at http://www.hbigda.org. The major purpose of the SOC is to articulate this organization's professional consensus about the psychological, medical and surgical management of gender identity disorders. These standards provide guidance to professionals practising in this area, who often work in isolation from mainstream medicine. It may also be of help in legal medicine to identify professional standards. Persons with gender identity disorders, their families and social institutions may use the SOC as a means to understand the current thinking of professionals.

Before initiating hormonal or surgical treatment that will change a person's gender, the physician should counsel the patient about realistic expectations from treatment. The only benefit sex reassignment can bring is relief of gender dysphoria; all human problems outside the area of gender dysphoria will remain. Unrealistic expectations that subjects may have of the success of hormonal and surgical treatment for their transition to the desired sex must be addressed. Contacts with other transsexuals who are already in the process of changing over to the new sex or who have completed this process may be helpful in shaping a subject's expectations of what can be achieved and what problems, personally and socially, may arise in the transition to the new sex.

II.4.8.1 Real Life Test

When hormone treatment starts, or maybe even earlier, the "real life test" should begin. It is an extended period of full-time living as a member of the desired sex. The "real life test" allows the subject and the attending professional to monitor the experience in the new sex status as he/she habituates his/her responses to other people. Without this test of how others react and how he/she reacts to others, the subject knows only his/her private convictions and fantasies of being a member of the opposite sex. Convictions and fantasies may be unrealistic and may lead to magical expectations of life in the new sex.

Embarking on the "real life test" may be done in a stepwise fashion; for instance, first in a trusted environment and later in public. The subject should have lived at least one full year full-time in the new sex before irreversible surgical reassignment is considered.

The "real life test" may be prolonged if too many hurdles present themselves during the test period. During the "real life test" the subject should stay in contact with a mental health professional to allow assessment of the success of the test and to discuss how to overcome problems that almost inevitably arise during this period.

II.4.8.2 Hormonal Sex Reassignment

Hormonal reassignment has two aims (Levy et al. 2003):

- To reduce the hormonally induced secondary sex characteristics of the original sex as much as possible, though complete elimination is rare. As an example, in male-to-female transsexuals, the previous effects of androgens on the skeleton, such as the greater height of men than women, the size and shape of hands, feet, jaws and pelvis, cannot be reversed. Conversely, the relatively lower height and the broader hip configuration of female-to-male transsexuals compared to men will not change with androgen treatment.
- To induce the secondary sex characteristics of the new sex.

II.4.8.2.1 Male-to-Female

To male-to-female transsexuals, elimination of sexual hair growth, induction of breast formation and a more female fat distribution are essential. To accomplish this, a near-complete reduction of the biological effects of androgens is required. Administration of oestrogens alone will suppress gonadotrophin output and therefore androgen production, but dual therapy with one compound that suppresses androgen secretion or action and a second compound that supplies oestrogen is more effective.

Suppression of Androgen Secretion or Action

Several agents are available to inhibit androgen secretion or action. In Europe, the most widely used drug is cyproterone acetate (usually 50 mg twice daily), a progestational compound with antiandrogenic properties. If it is not available, medroxyprogesterone acetate, 5–10 mg/day, is an alternative, although less effective. Nonsteroidal antiandrogens, such as flutamide and nilutamide, are also used, but they increase gonadotrophin secretion, causing increased secretion of testosterone and oestradiol; the latter is a desirable effect in this context. Spironolactone (100 mg twice daily), a diuretic with antiandrogenic properties, has similar effects. Long-acting gonadotrophin-releasing hormone (GnRH) agonists, used as monthly injections, also inhibit gonadotrophin secretion. Finasteride (5 mg/day), a 5-α-reductase inhibitor, might also be considered.

Oestrogen

There is a wide range of oestrogens from which to choose. Oral ethinyloestradiol (50–100 μg/day) is a potent and inexpensive oestrogen, but it may cause venous thrombosis, particularly in subjects over 40 years (van Kesteren et al. 1997; Moore et al. 2003; Toorians et al. 2003) and should no longer be used. Oral 17β-oestradiol valerate 2–4 mg per day or transdermal 17β-oestradiol, 100 μg twice a week, is the treatment of choice (Toorians et al. 2003).

Consequences

There are a variety of consequences of hormonal therapy in male-to-female transsexuals:

- Sexual hair – adult male beard growth is very resistant to inhibition by combined hormonal intervention, and in Caucasian subjects additional measures to eliminate facial hair are necessary. Sexual hair growth on other parts of the body respond more favourably (Giltay and Gooren 2000).
- Breast development – breast formation starts almost immediately after initiation of oestrogen administration and goes through periods of growth and standstill. Androgens have an inhibitory effect on breast formation and, therefore, oestrogens will be most effective in a milieu devoid of androgen action. After 2 years of oestrogen administration, no further development can be expected. It is quantitatively satisfactory in 40–50% of the subjects. The attained size is often disproportional to the male dimension of the chest and height of the subject, so the subject may desire surgical breast augmentation. Older age also impedes full breast formation.
- Skin – androgen deprivation leads to a decreased activity of the sebaceous glands, which may result in a dry skin or brittle nails (Giltay and Gooren 2000).
- Body composition – following androgen deprivation there is an increase in subcutaneous fat and a decrease in lean body mass. Body weight usually increases.
- Testes – lacking gonadotrophic stimulation, the testes become atrophic and may enter the inguinal canal, which may cause discomfort.
- Prostate – atrophy of the prostate may produce transient dribbling following micturition. This is usually temporary.

- Voice – antiandrogens and oestrogens have no effect on the properties of the voice, so male-to-female transsexuals may wish to consult a specialized phoniatric centre for speech therapy. Maleness of the voice is not so much determined by the pitch of the voice as by chest resonance and volume. Speech therapy may lead to more feminine speech (de Bruin et al. 2000). Laryngeal surgery may change the pitch of the voice but reduces its range.

Long-term Therapy

After reassignment surgery, including orchiectomy, hormone therapy must be continued. Some subjects still experience growth of sexual hair in a male pattern, and antiandrogens appear to be effective in reducing it, although the dose may be reduced. Continuous oestrogen therapy is required to avoid symptoms of hormone deprivation and, most importantly, to prevent osteoporosis (van Kesteren et al. 1998). We have found that oestrogens alone are capable of maintaining bone mass in male-to-female transsexuals. There was an inverse relationship between serum luteinizing hormone (LH) concentrations and bone mineral density, so serum LH may serve as an indicator of the adequacy of sex steroid administration.

II.4.8.2.2 Female-to-Male

The goal of treatment in female-to-male transsexuals is to induce virilization, including a male pattern of sexual hair and male physical contours, and to stop menses. The principal hormonal treatment is a testosterone preparation. The most commonly used preparations are testosterone esters in doses of 200–250 mg intramuscularly every 2 weeks. Recently, transdermal testosterone gels have become available. Occasionally menstrual bleeding does not cease with this regimen, and addition of a progestational agent is necessary. If a transdermal testosterone preparation is used, addition of a progestational agent is nearly always necessary.

Consequences

There are a variety of consequences of hormonal therapy in female-to-male transsexuals:

- Hair – the development of sexual hair follows essentially the pattern observed in pubertal boys: first the upper lip, then chin, then cheeks, etc. (Giltay and Gooren 2000). The degree of hirsutism can usually be predicted from the degree and pattern in male members of the same family. The same applies to the occurrence of alopecia androgenica.
- Voice – deepening of the voice occurs after 6–10 weeks of androgen administration and is irreversible. Androgen administration leads to a reduction of subcutaneous fat but increases abdominal fat. The increase in lean body mass is on average 4 kg, and the increase in body weight is usually greater.
- Acne – acne occurs in approximately 40 %, usually very pronounced on the back, similar to that observed in hypogonadal men starting androgen treatment past the age of normal puberty (Giltay and Gooren 2000).
- Clitoral enlargement – clitoral enlargement occurs in all, but the degree varies. In approximately 5–8 %, the size becomes sufficient for vaginal intercourse.
- Libido – most subjects will note an increase.
- Other – ovaries show polycystic changes, and androgen administration may decrease glandular activity of the breasts but does not reduce their size.

After bilateral oophorectomy, androgen therapy must be continued to maintain virilization and prevent osteoporosis (van Kesteren et al. 1998). Suppression of the serum LH concentration to within the normal range can be used to indicate the adequacy of androgen administration.

II.4.8.3 Side-Effects of Hormonal Sex Reassignment

In a review of 816 male-to-female transsexuals and 293 female-to-male transsexuals (total exposure 10,152 patient years), mortality was no higher than in a comparison group (van Kesteren et al. 1997). However, cross-sex hormone administration may be associated with side-effects (Futterweit 1998):

- Venous thromboembolism – the incidence of these side-effects was 2–6 % in male-to-female transsexuals treated with oral ethinyloestradiol. In vitro studies show that this thrombogenic effect is typical of oral ethinyloestradiol but not of oral 17β-oestradiol (Toorians et al. 2003). Because immobilization is also a risk factor for venous thromboembolic events, oestrogen administration should be discontinued 3–4 weeks before elective surgical interventions. Once subjects are fully mobilized again, oestrogen therapy may be resumed.
- Atherosclerosis – although the considerable sex difference in the prevalence of cardiovascular disease between men and women would lead one to expect an effect of hormonal treatment, the actual risk remains to be established. The effects of

oestrogen administration to male-to-female and of androgens to female-to-male transsexuals on biochemical risk markers have been studied. It appeared that oestrogen administration had more negative effects on these risk markers than androgens (Elbers et al. 2003).

- Lactotroph adenoma – four cases of lactotroph adenoma (prolactinoma) following high-dose oestrogen administration have been reported in subjects who had normal serum prolactin concentrations before therapy (van Kesteren et al. 1997). Though causality has not been established, we recommend that serum prolactin levels continue to be monitored in oestrogen-treated male-to-female transsexuals, also in the long-term.
- Breast cancer – there are two reports of male-to-female transsexuals who were found to have breast carcinomas while they were receiving oestrogen treatment (van Kesteren et al. 1997). In recent years no cases have been observed, but self examination of the breast must be part of the monitoring of oestrogen administration, following the same guidelines that exist for other women.
- Prostate cancer – three cases of prostate cancer in male-to-female transsexuals taking oestrogen have been reported (Van Haarst et al. 1998). It is not clear whether these cancers were oestrogen-sensitive or whether they were present before oestrogen administration started and progressed to become hormone-independent.
- Ovarian cancer – we recently observed two cases of ovarian carcinoma in a long-term, testosterone-treated, female-to-male transsexual. Ovaries of female-to-male transsexuals taking androgens show similarities with polycystic ovaries, which are also more likely to develop malignancies. Therefore, it seems reasonable to remove the ovaries of androgen-treated female-to-male transsexuals after a successful transition to the male role.
- Contraindications – because of the potential side-effects described above, hormonal treatment is contraindicated in certain situations. Contraindications to oestrogen use are a strong family history of breast cancer or a lactotroph adenoma, and to androgen-use lipid disorders with cardiovascular complications. Contraindications against the use of high doses of either sex steroid are cardiovascular disease, cerebrovascular disease, thromboembolic disease, marked obesity, poorly controlled diabetes mellitus, and active liver disease (Futterweit 1998; Levy et al. 2003; Moore et al. 2003).

II.4.8.4 Juvenile Gender Dysphoria

Adult transsexuals often recall that their gender dysphoria started early in life, well before puberty. Children with gender identity problems increasingly come to the attention of the psychomedical care system. A reliable estimation indicates that only about 20% will become transsexuals in adolescence (Cohen-Kettenis and van Goozen 1998). Homosexuality will be more often the outcome.

If, in expert opinion, a child's cross-sex gender identity will not change during long-term follow-up the individual may be spared the torment of (full) pubescent development of the "wrong" secondary sex characteristics (Cohen-Kettenis and van Goozen 1998). Depot forms of luteinizing hormone releasing hormone (LHRH) antagonists/agonists, following the regimen in children with precocious puberty, can be used when clear signs of sexual maturation are evident in order to delay pubertal development until an age that a balanced and responsible decision can be made to transition to the other sex (Gooren and Dellemarre van de Waal 1996).

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II.4.9 Treatment of Sexual Dysfunction

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Summary

The introduction of the phosphodiesterase type 5 inhibitors (PDE inhibitors) has been a major step forward in the treatment of erectile dysfunction (ED). Though efficacious and safe, 50% of men discontinue treatment, largely because other sexological issues have not been properly addressed. To predict onset and duration of action, insight into the pharmacokinetics of the PDE inhibitors is required.

- In men whose testosterone levels are low, testosterone substitution may booster the efficacy of PDE inhibitors.
- Before receiving PDE inhibitor the cardiovascular status of a patient must be assessed.

The main action of testosterone is on the central nervous system. It improves libido and mood. Levels in the low-normal range suffice.

Hyperprolactinaemia impairs sexual interest and leads to secondary ED. Dopamine agonists are the treatment of choice.

Men with paraphilias may be treated with drugs that lower androgen action if the desire to act out their paraphilia is high.

II.4.9.1 Erectile Dysfunction

The availability of a highly efficacious and relatively safe compound such as the phosphodiesterase type 5 inhibitor sildenafil has had a profound impact on diagnosis and treatment of erectile dysfunction (ED). Once the domain of the urologist attempting to define the precise aetiology, ED is now largely treated by first-line physicians, without much of a diagnostic work-up. Despite the simplicity and safety of the present therapy of ED, approximately 50% of patients discontinue treatment. The reasons for discontinuations lie mostly in an incomplete evaluation of the sexual problem. Hypogonadism, ejaculatory dysfunction, lower urinary tract symptoms, depression, and last but not least partner issues may all be components of the sexual dysfunction of the patient, and apparently restoration of erectile function does not necessarily imply restoration of a happy sex life (Montorsi and Althof 2004). Nevertheless, the introduction of the phosphodiesterase type 5 inhibitors has substantially improved the therapeutic options for ED.

II.4.9.1.1 Phosphodiesterase Type 5 Inhibitors

The identification of pathways in the physiology of erection and the discovery of the importance of nitric oxide (NO) and its downstream effects lie at the basis of the development of the phosphodiesterase type 5 inhibitors (PDE inhibitors). Subsequent to sexual stimulation, NO arising from the nerve endings of non-adrenergic non-cholinergic innervation of the corpus cavernosum activates guanylyl cyclase, an enzyme that catalyses the conversion of GTP to cGMP. At the cellular level cGMP is broken down to 5-GMP by phosphodiesterase type 5. Via a molecular cascade cGMP lowers intracellular calcium and vascular smooth muscle of the corpus cavernosum relaxes, resulting in an increased penile blood flow thus facilitating the initiation and maintenance of an erection.

The pharmacological action of PDE inhibitors manifests itself only when a person is sexually aroused, which distinguishes this class of drugs from intracavernosal injections. This is also important information for the user (Seftel 2004).

The efficacy and relative safety of PDE inhibitors is well documented now. They have a common mode of action, the inhibition of PDE 5. Selectivity and tissue localization of the PDE inhibitors determine the side-effect profiles and safety.

There are presently three PDE inhibitors available for prescription: sildenafil, vardenafil and tadalafil. All are efficacious, but there are differences in pharmacokinetic profile, interactions with food and drugs, and possible side-effects. Taking nitrate medications is an absolute contraindication to the use of PDE inhibitors since PDE inhibitors increase the potential for excessively low blood pressure. Low blood pressure, though to a lesser degree, has also been observed with PDE inhibitors in men taking alpha adrenoreceptor antagonists, such as doxazosin, prazosin, terazosin, alfuzosin

or tamsulosin, which are used as antihypertensive agents or for symptomatic relief of lower urinary tract symptoms (LUTS). The latter is relevant since sexual dysfunction is not rare in men with LUTS, both significantly increasing with age, and possibly sharing aetiological factors (Rosen et al. 2003). Drugs such as erythromycin, ketoconazole and itraconazole, and protease inhibitors used in HIV treatment such as saquinavir, indinavir and ritovir may slow liver metabolism of PDE inhibitors and may increase plasma levels and the effect of PDE inhibitors. Grapefruit juice may have a similar effect on liver metabolism. Lower doses must be used in patients with liver and/or kidney disease.

Sildenafil and vardenafil work best if no (fatty) food has been taken within the previous 2 h, while tadalafil can be used without regard to food.

Common adverse effects attributable to vasodilatory effects include headache, flushing, stuffy nose, stomach pain, back pain (tadalafil) and indigestion. Visual problems (for example, blurred vision, increased sensitivity to light, bluish haze, or temporary difficulty distinguishing between blue and green) may occur, more often with sildenafil since the latter is less selective in inhibiting phosphodiesterase 6 in the retina.

The prescribed tablet strength is swallowed 30–60 min before sexual activity. Tadalafil has a longer duration of increased sensitivity for developing an erection (up to 24–36 h) compared with sildenafil and vardenafil (up to 4–12 h).

There is no convincing evidence that the three available PDE inhibitors differ significantly in their clinical efficacy. For sildenafil (50 and 100 mg) and tadalafil (10 and 20 mg) there is a dose–response relationship, which is not so much the case for vardenafil (10 and 20 mg) (Carson et al. 2004). In general starting with the lowest dose of PDE inhibitors is recommended.

The feature that distinguishes the three PDE inhibitors is their pharmacokinetic profile, which impacts on their clinical use, in terms of the initiation of optimal pharmacological effect and duration of pharmacological action [for review see Porst (2004)]. The time to maximal plasma concentration (in minutes) is on average 60 (variation 30–120) for sildenafil, 120 (variation 30–720!) for tadalafil and 60 (variation 30–120) for vardenafil. These are statistical data and individual patients may experience a faster onset of action. This information lets patients plan prospective sexual action. Another significant pharmacokinetic variable is the half-life of the drug, which provides an indication of how long the drug can be expected to be pharmacologically active after ingestion. The half-life of sildenafil 100 mg is 3–4 h; for tadalafil, 20 mg 17 hours; and for vardenafil, 3–6 h. This information lets the patient make reasonable assumptions about how long they can expect the ingested compound to be pharmacologically active.

It is not rare for patients to wish to "experiment" with the available PDE inhibitors to find the drug that suits them best. Patients do have distinctly different sexual habits with regard to timing of sexual activity. Another consideration is the "readiness" of the patients when sexual activity is initiated by the partner.

The above information on dose–response effects (sildenafil and tadalafil), the interaction with (particularly fat-rich) food in slowing absorption, and the pharmacokinetic profiles may provide guidance. Patients who, in a series of at least four attempts to have intercourse, do not respond to the maximum dose of one of the PDE inhibitors are unlikely to respond to the others.

Naturally, patients starting treatment with a PDE inhibitor will experience some anxiety about whether the new drug will indeed induce an erection. Anxiety may reduce sexual arousal, which is a necessary condition for the desired pharmacological action of PDE inhibitors. Therefore, in case the patient recognizes this as a potential problem, testing the efficacy of the drug first with masturbation may be recommended.

At least 50% of patients suffering from ED have endothelial dysfunction, and there are early indications that chronic treatment with PDE inhibitors might improve their vascular function (Jackson 2003; Reffelmann and Kloner 2003). At the same time chronic use would obviate the need to take a PDE inhibitor before engaging in sexual activity.

II.4.9.1.2 PDE Inhibitors and the Cardiovascular System

When the first PDE inhibitor sildenafil was introduced there was great concern about the cardiovascular safety of this class of drugs. In many a patient the aetiology of ED is (also) based on vascular disease. The availability of the drug prompted patients to resume sexual activity after prolonged periods of inactivity. The pharmacological action of PDE inhibitors is vasodilatory. Fears arose that these elements would lead to myocardial ischaemia or infarction when intercourse was attempted. Fortunately, these concerns have remained unsubstantiated. Placebo-controlled studies fail to show a higher cardiovascular morbidity/mortality in patients using PDE inhibitors (Hutter 2004; Kloner 2004). Naturally, before starting PDE inhibitors, the cardiovascular risks of the patient must be assessed. Factors such as hypertension, biochemical risk markers, angina pectoris, arrhythmias, cardiomyopathy, congestive heart failure and a history of myocardial infarction and the time elapsed since and whether these conditions are adequately treated must be weighed. The Princeton Consensus Panel has drafted an algorithm for stratification of cardiac patients as being at low, intermediate or high risk of using PDE inhibitors for ED (DeBusk et al. 2000;

Seftel 2004; Seftel et al. 2004). Patients with intermediate and high risks may benefit from a cardiological evaluation to optimize their cardiac condition. A rule of thumb indicator is whether a patient can walk 1 km in 10 min without cardiac symptoms, an equivalent of the physical exertion of sexual intercourse.

Patients should be instructed to report use of a PDE inhibitor in the foregoing 24 h (sildenafil / vardenafil) or 48 h (tadalafil) when a cardiovascular emergency occurs that might need treatment with nitrates.

II.4.9.1.3 Centrally Acting Oral Agents

Increasing understanding of the physiology of erections and particularly the role of the central nervous system has led to the development of apomorphine hydrochloride. This compound targets structures in the central nervous system associated with erectile function. Apomorphine is a non-specific dopaminergic receptor agonist that acts at the paraventricular nucleus of the hypothalamus (Altwein and Keuler 2001; Martinez et al. 2003). Apomorphine is available in a sublingual formulation at doses of 2 and 3 mg. Apomorphine is a fast acting agent (maximum plasma concentrations at 15 – 20 min) that has been shown in various clinical trials to be more effective at achieving erections firm enough for intercourse compared to placebo. But its efficacy is less than that of the PDE inhibitors (Heaton and Altwein 2001). Side-effects have been reported in clinical trials. At 6 mg dosages of apomorphine nausea has been reported in up to 34 % of patients (Bukofzer and Livesey 2001). At the approved dosage of 2 and 3 mg the incidence of nausea decreases to only 7 %. Other significant known side-effects include headache, dizziness and yawning.

II.4.9.1.4 Intracavernosal Agents

Nowadays before patients resort to intracavernosal therapy, they have usually tried oral therapy unsuccessfully. For intracavernosal injections a patient or his partner must possess adequate manual dexterity to carry out the penile injections. Patients must receive information on the potential adverse effects of the injections. Side-effects include penile scarring, pain, ecchymosis and prolonged erection. The incidence of these side-effects depends on the agent injected. The most common agents used in practice include prostaglandin E_1, papaverine and phentolamine, and the α-blocker moxisylyte.

Phentolamine, which is an alpha adrenergic antagonist, has a very poor erectile response in humans when used on its own. It is therefore usually combined with either papaverine alone (Bimix) or with papaverine and prostaglandin E_1 (Trimix). Papaverine is a non-specific phosphodiesterase inhibitor that causes an increase in both intracellular cAMP and cGMP. Increases in these molecules cause a relaxation in penile smooth muscle and eventual erection.

Prostaglandin E_1 modulates adenyl cyclase to increase cAMP concentrations. This in turn leads to a decrease in intracellular free calcium and smooth muscle relaxation in the penis (Porst 1996). Although prostaglandin E_1 leads to significantly fewer occurrences of penile fibrosis and priapism, some studies quote a 13 % incidence of penile pain with injection of this medication. In an effort to reduce the adverse effects of these medications used alone, combination therapy with a mixture of phentolamine, papaverine and prostaglandin E_1 (Trimix) at lower doses often will provide a higher efficacy, lower incidence of pain and lower cost per dose (Bennett et al. 1991).

II.4.9.1.5 Intraurethral Agents

Prostaglandin E_1 (PGE_1) (trade name MUSE) is the most common agent used for this purpose, and by delivering the active compound into the urethra there is transportation of the compound into the corpus spongiosum and later into the corpora cavernosum where smooth muscle relaxation occurs.

Efficacy rates are variable: from a 13.6 % response to a 64 % response (when a constriction band is used) (Hellstrom et al. 1996). The most common side-effect of intraurethral agents is local penile pain which occurs in more than one-third of patients. Urinary tract infection, dizziness, penile pain and urethral bleeding are other known side-effects.

II.4.9.1.6 Non-pharmacologic Treatment

Non-pharmacologic options may be offered as second-line treatment in lieu of intraurethral or intracavernosal injection for patients who do not respond to or cannot tolerate oral therapy. Vacuum erection devices increase corporal blood flow, and a constrictor ring is then used to retain this blood within the penis. Satisfaction is variable (27 – 74 %), and this technique can cause discomfort and bruising of the penis (Hatzichristou and Pescatori 2001).

Surgical options exist for patients with ED. Penile arterial bypass surgery is appropriate in only a select group of patients (men under 35 years of age who have no generalized vascular disease and in whom an isolated injury has obstructed blood flow). Penile implants are available for patients who have not responded to more conservative treatment. This procedure is invasive, irreversible and subject to complications such as

infection, erosion and mechanical failure. There is, however, a high rate of patient and partner satisfaction (Hatzichristou and Pescatori 2001).

II.4.9.2 Retarded Ejaculation

Retarded ejaculation is not infrequent in the ageing male. It may be related to a decrease in sexual arousability, often associated with ageing. In general, measures to improve erectile function will also benefit retarded ejaculation. It is also often found in men with lower urinary tract symptoms and there is some preliminary evidence that an alpha adrenoreceptor blocker such as alfuzosin might alleviate the complaint. It may be associated with the use of psychotropic drugs such as serotonin reuptake inhibitors and monoamine oxidase inhibitors.

II.4.9.3 Rapid Ejaculation

Rapid or premature ejaculation is difficult to treat (Waldinger 2004). The complaint may be presented as ED by patients who are unable to attain sufficient penile rigidity after rapid ejaculation. Several oral agents, such as selective serotonin reuptake inhibitors, monoamine oxidase inhibitors and tricyclic antidepressants (e.g. imipramine and clomipramine) or topical anaesthetic agents (e.g. lidocaine) have been recommended (Montague et al. 2004). Of late sildenafil has also been helpful. Sexual counselling may help the patient to have better control of the ejaculatory response.

II.4.9.4 Testosterone Treatment

The evidence for testosterone-induced masculinization of certain aspects of sexual behaviour in men is persuasive. Although clinicians have long been impressed with the influence of androgen replacement on sexual functioning of androgen-deficient men, scientific proof that androgen plays a role in human sexuality is a product of the 1970s and 1980s (Bancroft 2002).

Most of the information has been collected from androgen withdrawal/replacement studies of hypogonadal men. It is now clear that androgens are fundamental to normal sexual behaviour in men, although they do not have a simple on/off effect on sexual functions, and are not the only factor involved in male sexual behaviour (Gooren and Kruijver 2002).When androgen production is deficient from the foetal/prepubertal stage, as in hypogonadotrophic hypogonadism and Klinefelter syndrome, the response to androgen replacement during puberty or later may be manifestly impaired, expressing itself as relative sexual inertia. The reason probably is that emotional, cognitive and social learning are also elements of the manifestations of testosterone on adolescent and adult sexuality (Gooren and Kruijver 2002).

The distinction between sexual interest and erectile function and its subdivision has helped considerably in clarifying the role of androgens in male function (Bancroft and Wu 1983; Bancroft 2002).

Spontaneous erections, particularly those that occur during sleep (nocturnal penile tumescence, NPT), and probably fantasy-induced erections are androgen-dependent, whereas erections in response to erotic (e.g. visual or tactile) stimuli are relatively androgen-independent (Bancroft and Wu 1983). These early studies addressed, however, maximum increase in penile circumference as the only parameter, but more recent work suggests that androgens affect penile responses to erotic stimuli with regard to duration of response, degree of rigidity and speed of detumescence (Carani et al. 1996). In men the principal target of androgens appears to be sexual interest or appetite (Bancroft and Wu 1983; Bancroft 2002). Androgens may enhance the persistence of attention to eroticism, which, in turn, may affect sexual behaviour. It has been argued that androgen influences pleasurable awareness during sexual activity, possibly by enhancing sensory (genital) function.

It is not known how the effects of androgens on the central nervous system are mediated. Preliminary evidence suggests that there may be a noradrenergic mediation of sexual arousal, involving both central arousal and peripheral inhibition of erectile responses (Bancroft 1995).

Although it has been convincingly established that the main effect of androgens on male sexual functioning is on the central nervous system, additional evidence now suggests that they also affect nitric oxide synthase in the corpus cavernosum [nitric oxide induces smooth muscle relaxation of the penile vasculature, essential for penile erection (Morelli et al. 2004)] and that androgen administration may be helpful in men who respond poorly to treatment of ED with phosphodiesterase inhibitors (Foresta et al. 2004). So there seems to be a point in treating men with low or low–normal plasma testosterone, who do not respond well to phosphodiesterase inhibitors, with testosterone.

In most studies, 60–70% of the reference values of testosterone were sufficient to maintain sexual functions in adult men (Gooren 1987; Buena et al. 1993). One study suggested that thresholds for NPT are even lower than those for normal sexual functioning (Carani et al. 1996). From this it follows that in men with sexual dysfunction and normal androgen levels, additional testosterone is likely to be of no help, although a short-lived beneficial effect from additional testosterone in eugonadal men who complained of lack of sexual interest has been found (Anderson et al. 1992) and con-

firmed in men receiving testosterone in a male contraceptive study (Alexander et al. 1997), but the follow-up was limited to 6 weeks. There is no evidence that long-term high testosterone levels enhance male sexual function. In general it has been difficult to establish a relationship in men between circulating testosterone levels (above a certain therapeutic threshold) and levels of sexual responses (Gooren 1987; Buena et al. 1993).

Information on the timing of onset of behavioural effects after withdrawal of androgens is limited. With both naturally occurring and pharmacologically induced hypotestosteronaemia, behavioural effects and a reduction in seminal emission become clear after 2 weeks and reach a maximum after 4 weeks or later. A sexually active partner may be a factor in prolongation of sexual activity (Bancroft 2002). In the majority of men the ejaculatory capacity is profoundly decreased after androgen withdrawal, affecting sexual behaviour in its own right (Bancroft 2002).

Restoration of testosterone effects is probably somewhat quicker, approximately over 1 – 2 weeks, and there may be a relationship with the duration of foregoing androgen deficiency (Bancroft 2002).

Testosterone is currently available in oral, intramuscular, subcutaneous and transdermal preparations. Recent advances in testosterone replacement therapy include testosterone gels, which provide flexibility in dosing and minimal skin irritation resulting in good compliance, and the development of longer acting intramuscular preparations (testosterone undecanoate), which result in more stable testosterone levels with longer injection intervals up to 12 weeks (Gooren and Bunck 2004).

In summary, it is certain that androgens are powerful modulators of the biochemistry of peripheral structures related to sexual functioning and the brain, thus modulating behaviour. Their effects are strongly intertwined with idiosyncratic aspects of the person concerned: they enhance sexual motivation in men, be it a heterosexual, homosexual or paraphilic man. The blood level of testosterone critical for normal male sexual function varies between individuals. In most males, 60 – 70 % of the reference values was sufficient (Gooren 1987; Buena et al. 1993). In men with sexual dysfunction and normal androgen levels, additional testosterone is likely to be of no help, although a short-lived beneficial effect from additional testosterone in eugonadal men who complained of lack of sexual interest has been found.

II.4.9.5 Pubertal Development

Pubertal development is associated with a gradual though variable increase in sexual interest and activity, but it has been difficult to relate levels of androgens to the development of adolescent sexuality, probably because there is a fair but individually different amount of socially influenced learning which impacts on this hormone–behaviour relation. Physical pubertal development may be a better predictor of sexual interest and behaviour than free testosterone (Finkelstein et al. 1998; Halpern et al. 1998) but one study was able to demonstrate a more direct relationship between salivary/plasma testosterone and sexual activity (Udry et al. 1985).

II.4.9.6 Sexual Function and Ageing

Sexual functions decline with ageing. Ageing as such is the best predictor of ED, with diabetes mellitus and atherosclerotic cardiovascular diseases further increasing the risk (Johannes et al. 2000).

Ageing is also associated with a variable decline in bioavailable testosterone levels, but levels remain well above minimum testosterone levels for normal sexual functioning established in younger men. The hypothesis has been advanced that ageing men are less sensitive to the actions of testosterone (Schiavi and Rehman 1995), but as indicated above testosterone is not the first-line treatment in elderly men with ED, but it may be adjuvant treatment when phosphodiesterase inhibitors are not helpful and plasma testosterone is low.

II.4.9.7 Hyperprolactinaemia

The role of prolactin in males is not well understood. No convincing evidence has emerged that a lower than normal prolactin level impairs sexual functioning in humans (Carani et al. 1996). In women the initial symptom of hyperprolactinaemia is mostly a disturbance in reproductive physiology (amenorrhoea, infertility), leading to a relatively early discovery of the condition. Interference with female sexual functioning has been reported but is less clear-cut than in men. It may be manifested as a depressive disorder affecting orgasmic capacity, which improves upon treatment with dopamine agonists.

In men, sexual dysfunction, but more often symptoms of a pituitary tumour may lead to the discovery of hyperprolactinaemia. This condition accounts for less than 2 % of cases of sexual dysfunction in men (Carani et al. 1996). About 80 – 90 % of men with chronic hyperprolactinaemia have complaints such as loss of libido, erectile weakness (De Rosa et al. 2004) and, frequently, difficulty ejaculating (Meston and Frohlich 2000). The mechanism by which hyperprolactinaemia impairs sexual function is not completely understood. In cases of associated testosterone deficiency, testosterone substitution did not reverse the symptoms (Carani et al.

1996). Dopaminergic drugs restored sexual function even before testosterone levels had risen to normal (De Rosa et al. 2004).

Most experts now believe that hyperprolactinaemia impairs sexual function through a CNS mechanism by interference with neurotransmitter activity, in particular dopamine and endogenous opioids (Meston and Frohlich 2000). In some men with sexual complaints, serum prolactin levels may be found to be elevated in the presence of normal gonadotrophin and testosterone levels. They may have macroprolactinaemia, and their sexual problems cannot be ascribed to their spurious hyperprolactinaemia (Schlechte 2002).

Administration of antipsychotic drugs is not rarely associated with marked hyperprolactinaemia. And it is increasingly clear that this drug-induced hyperprolactinaemia may produce galactorrhoea, gynaecomastia, sexual dysfunction and mood disturbances (Halbreich et al. 2003). The condition is often not diagnosed since the psychological effects are viewed as part of the disease requiring antipsychotic medication. In cases of clinically relevant hyperprolactinaemia, the dose of the antipsychotic drug may be lowered or an alternative drug must be chosen.

II.4.9.8 Paraphilias and their Pharmacologic Treatment

Persons with a paraphilia are compulsively responsive to and dependent on an unusual and often personally or socially unacceptable sexual stimulus for sexual arousal and orgasm. No known correlation between paraphilic behaviour and an endocrine condition, past or present, has been detected (Gijs and Gooren 1996). Paraphilias occur predominantly in men but also may occur in women. There is no convincing evidence that circulating testosterone levels are higher in (violent) sex offenders than controls (Gijs 1996). The socially intolerable paraphilias (such as rape, exhibitionism and paedophilia) may bring persons into conflict with the law, and (forensic) medicine may play a part in pharmacological interventions aimed at helping paraphiliacs. When dealing with this category it is mandatory to observe professional neutrality. As in normal persons, testosterone lowers the threshold of occurrence of erotosexual imagery and sexual activity in paraphiliacs. However, it has no effect on the contents of the imagery (Gijs and Gooren 1996). Anti-androgens may be of benefit, particularly for those paraphilias characterized by intense and frequent sexual desire and arousal. To be effective, hormonal treatment must be accompanied by sexologic counselling. The most widely used drug in the United States is medroxyprogesterone acetate, and in Canada and Europe cyproterone acetate. Luteinizing hormone-releasing hormone (LHRH) agonists have also been successfully used (Reilly et al. 2000). Both are available in injectable form, thus facilitating greater compliance with the treatment programme. Long-term androgen deprivation may lead to osteopenia (Grasswick and Bradford 2003). Some forms of paraphilia are not so much characterized by sexual desire but are obsessive-compulsive or impulse control disorders or are acted out in depressive mood states, and do not respond well to anti-androgenic intervention. These can be successfully treated with psychotropic drugs such as modern antidepressants in view of the role of the dopaminergic system in motivational processes.

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II.4.10 Therapeutic Options for Benign Prostate Hyperplasia (BPH) and Prostatic Cancer

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Summary

The management of symptomatic benign prostate hyperplasia (BPH) includes:

- Watchful waiting – suitable management of patients with mild symptoms of BPH (International Prostate Symptom Score, IPSS ≤ 7) or patients with moderate or severe symptoms (IPSS ≥ 8) but with minimal bother.
- Medical therapy – suitable management of patients with moderate or severe symptoms with bother.
- Alpha-blockers – alfuzosin, tamsulosin, terazosin and doxazosin are similarly effective and have quicker onset of action.
- 5α-Reductase inhibitors – finasteride and dutasteride are suitable for patients with lower urinary tract symptoms (LUTS) associated with demonstrable prostatic enlargement but the onset of action is slower.
- Combination therapy – combination of alpha-blocker and a 5α-reductase inhibitor suitable in patients with LUTS associated with demonstrable prostatic enlargement.
- Minimally invasive therapy – thermal, radiofrequency or laser are the energy sources used. The efficacies of these modalities are not conclusively proven yet.
- Surgical therapy – suitable for patients who have bothersome symptoms and for those who have developed complications of BPH. This may be open or endoscopic surgery.

The management of locally advanced prostate cancer includes:

- Active monitoring – suitable for patients with low volume and well differentiated prostate cancer with less than 10 years of life expectancy.
- Radical prostatectomy – suitable for patients with localized prostate cancer with more than 10 years of life expectancy.
- Radical radiotherapy – suitable for patients with localized prostate cancer and the results are comparable to those for radical prostatectomy.
- Brachytherapy – suitable for patients with localized low-grade small volume prostate cancer.

The management of locally advanced prostate cancer and metastatic disease includes:

- Surgical castration – the procedure is well tolerated and is effective at lowering testosterone.
- Oestrogen – decrease dosing decreases the risk of cardiovascular toxicity but testosterone levels do not fall to castration levels.
- Luteinizing hormone releasing hormone agonist (LHRHa) – as effective as surgical castration in lowering testosterone levels but can cause an initial flare in tumour growth and therefore initiation of therapy should be covered with 4 weeks of anti-androgen therapy.
- Non-steroidal anti-androgens – bicalutamide is currently being evaluated for monotherapy use in the management of advanced prostate cancer.
- Steroidal anti-androgens – cyproterone acetate causes a decrease in serum androgens and therefore may reduce libido and sexual potency.
- Maximal androgen blockade – patients with severe symptoms due to local cancer spread or metastatic disease or very high prostate specific antigen (PSA) and alkaline phosphatase may achieve quicker symptom control.

The management of hormone relapsed prostate cancer includes:

- Anti-androgen withdrawal – withdrawal of anti-androgen may improve clinical symptoms.
- Second-line hormonal therapy – agents such as oestrogens and steroids may provide a useful symptomatic response.
- Cytotoxic chemotherapy – there are a number of agents evaluated with initial promising results.
- Palliative management – bone pain can be alleviated with local radiotherapy or intravenous strontium. Zoledronic acid, a bisphosphonate, reduces bone pain and delays the onset of skeletal complications. Spinal cord compression is an emergency and is treated with high-dose steroids, local radiotherapy, surgical decompression or percutaneous vertebroplasty.

II.4.10.1 Diagnosis

II.4.10.1.1 Symptoms

- Obstructed symptoms – hesitancy, weak stream, straining, feeling of incomplete emptying and overflow incontinence.
- Irritative symptoms – urgency, frequency, nocturia and urge incontinence.
- International Prostate Symptom Score (IPSS) – structured questionnaire for the assessment of lower urinary tract symptoms (LUTS): mild (0 – 7), moderate (8 – 19) and severe (20 – 35).

The challenge is to establish whether the symptoms are due to benign prostate hyperplasia (BPH) as there are many non-prostatic causes of LUTS. Initial evaluation should start with a general medical history regarding general health, medical conditions that lead to bladder dysfunction or excessive urine production, and family history of prostate disease (BPH and prostate cancer). A specific urinary tract history should also be taken and this would focus on BPH symptoms such as hesitancy, frequency, nocturia, post-micturition dribbling, haematuria, urinary tract infection and urinary retention. The patient's medication needs to be reviewed for drugs that may affect bladder function such as anticholinergics (e.g. chlorpheniramine), which may impair bladder contractility, and α-sympathomimetics (e.g. pseudoephedrine), which may increase outflow resistance.

Several structured symptom questionnaires have been developed, points being assigned for each answer and the sum of which comprises the symptom score. The IPSS (Barry et al. 1992) is the most widely used and recommended questionnaire for the assessment of

Table II.4.3. International Prostate Symptom Score (IPSS) questionnaire with quality of life question

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your score
1. Incomplete emptying Over the past month, how often have you had a sensation of not emptying your bladder completely after you finish urinating?	0	1	2	3	4	5	
2. Frequency Over the past month, how often have you had to urinate again less than 2 h after you finish urinating?	0	1	2	3	4	5	
3. Intermittency Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Urgency Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Weak stream Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Straining Over the past month, how often have you had to push or strain to begin urination?	0 None	1 1 time	2 2 times	3 3 times	4 4 times	5 5 or more times	
7. Nocturia Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0	1	2	3	4	5	
Total symptom score							

Quality of life due to urinary symptoms	**Delighted**	**Pleased**	**Mostly satisfied**	**Mixed – equally satisfied**	**Mostly dissatisfied**	**Unhappy**	**Terrible**
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about it? (Circle number)	0	1	2	3	4	5	6

LUTS associated with BPH (Denis et al. 1998). It consists of seven questions relating to the symptoms of BPH and one further quality of life question (Table II.4.3). By using this system, the symptoms can be classified as mild (0–7), moderate (8–19) or severe (20–35). However, the IPSS does not correlate well with other indices of lower urinary tract dysfunction (e.g. flow rates) but is a useful tool for obtaining baseline symptom severity, assessing the response to treatment and detecting the progression of symptoms in patients managed by watchful waiting.

II.4.10.1.2 Physical Examination

- Digital rectal examination (DRE) – simple and cost-effective method for assessing the prostate (size, consistency and surface texture are noted).
- PSA – performed for patients in whom the diagnosis of prostate cancer would alter management. A level of ≥4 ng/ml is abnormal but there are age-specific reference ranges.
- Uroflowmetry – this is an electronic measurement of urinary flow and the lower the maximum flow rate, the higher the probability of bladder outlet obstruction.
- Pressure-flow studies – this invasive test differentiates between patients with detrusor failure (e.g. due to neuropathic disease) and bladder outlet obstruction.
- Urethrocystoscopy – invasive test to allow visualization of the lower urinary tract.
- Transrectal ultrasound of prostate – allows assessment of size and shape of prostate to plan invasive treatment and is used to guide needle biopsies of the prostate.
- Upper tract imaging – useful to rule out upper tract pathology if the patient has reported haematuria or urea and creatinine are deranged.

The abdomen should be carefully examined to assess whether a full bladder is palpable and whether there is evidence of phimosis, which may obstruct urinary flow. DRE is a simple method for assessing prostate health. The normal prostate is about the size of a walnut and has the same rubbery consistency as the tip of the nose. Symmetrical enlargement with a smooth and elastic consistency and preservation of the midline sulcus is consistent with BPH. However, prostate cancer may result in a nodular prostate that can be stony and asymmetrical. A tender prostate suggests prostatitis. DRE tends to underestimate the volume of the prostate especially in those greater than 30 ml (Roehrborn et al. 1997).

II.4.10.1.3 Investigations

Urinalysis should be performed by dipstick testing or by microscopic examination to screen for haematuria or urinary tract infection (UTI). Bladder cancer, carcinoma in situ of the bladder, UTIs, urethral strictures and bladder stones can produce LUTS in men. Although pyuria or haematuria is not always present in these conditions, a normal urinalysis makes these diagnoses less likely (Messing et al. 1992).

The measurement of serum creatinine has been recommended in patients with LUTS. This is to rule out renal insufficiency caused by obstructive uropathy (Denis et al. 1998). It may also be necessary to check the creatinine values prior to imaging studies that require intravenous contrast. Also it is well established that patients with a degree of renal insufficiency have a higher risk of post-operative complications (Mebust et al. 1989).

Prostate cancer can also occur in patients with BPH. Measurement of PSA should be performed for patients for whom the detection of prostate cancer would alter management. This measurement should not be performed soon after DRE as PSA may be falsely elevated (Lechevallier et al. 1999). Some physicians consider a PSA level of greater than 4 ng/ml abnormal whereas others use age-specific reference ranges which reflect the fact that prostate size and PSA increase with age. Age 50–59, 3.5 ng/ml; age 60–69, 4.5 ng/ml; age 70–79, 6.5 ng/ml (Oesterling et al. 1993). However it is the rapid increase in PSA with time that is a particularly alarming and reliable sign of cancer development. Undertaking both PSA and DRE is a relatively sensitive way to exclude prostate cancer as a diagnosis. Unfortunately, PSA is not a specific test for prostate cancer as approximately 25% of men with BPH have a serum PSA greater than 4 ng/ml. Due to this overlap in serum PSA in men with BPH and clinically localized prostate cancer, PSA velocity, free/total PSA ratio, complexed PSA (cPSA), and PSA density measurements have been developed in attempts to improve diagnostic specificity (Mikolajczyk et al. 2002). It is also known that patients with higher serum PSA have a higher risk of future growth of the prostate, worsening symptoms, decrease in flow rate, acute urinary retention and BPH-related surgery (Roehrborn et al. 1999, 2000, 2001).

II.4.10.1.4 Additional Diagnostic Tests

Patients with a normal initial evaluation and mild symptoms that are not bothersome do not usually require further investigation or treatment. They may be offered advice on lifestyle and fluid intake and discharged. Those with more bothersome symptoms should be assessed further using the additional tests outlined here.

II.4.10.1.5 Urinary Flow Rate

This is measured with a flowmeter and is an electronic measurement of urinary flow throughout the course of micturition. Modern flowmeters produce not only a flow trace but also a printout of the important parameters (Fig. II.4.31). Flow rate measurements on a voided volume of less than 150 ml may not provide a true indication of the patient's flow, as the maximum flow rate increases with volume up to this point (Drach et al. 1979). The peak flow (Q_{max}), measured in millilitres per second, identifies patients with BPH more specifically than average flow rate (Q_{ave}) (Gleason et al. 1982). Maximum urinary flow rates have been shown to decrease gradually with age and a Q_{max} of between 10 and 15 ml/s may be considered normal in men aged 70 – 80 years (Girman et al. 1993). Symptoms and symptom score analysis do not correlate strongly with uroflowmetry measurements and, due to test and re-test variability, there is not a flow rate "cut off point" for decision making.

II.4.10.1.6 Post Void Residual

Post void residual (PVR) is defined as the amount of urine left behind in the bladder after micturition. The PVR is usually measured with transabdominal ultrasound but can be measured invasively with catheterization. Large variations in measurements of PVR in the same patient have been documented (Bruskewitz et al. 1982). Most clinical studies have demonstrated that PVR correlates poorly with other signs and symptoms of BPH (Abrams and Griffiths 1979) although a PVR >50 ml has been shown to be associated with a threefold increase in the risk of acute urinary retention (Jacobsen et al. 1997).

II.4.10.1.7 Pressure-Flow Studies

The recording of detrusor pressure during bladder filling and voiding requires either urethral or suprapubic catheterization. Pressure-flow studies or urodynamic studies differentiate between the patients who have detrusor failure and those who have bladder outlet obstruction (BOO). They should be considered in patients in whom the initial evaluation, uroflowmetry and PVR cannot confirm BOO, particularly when invasive therapy is being considered (Denis et al. 1998). Pressure-flow studies are also useful in patients with neurological disease whose LUTS may have detrusor failure or in patients who have not responded to previous treatment. The key measure-

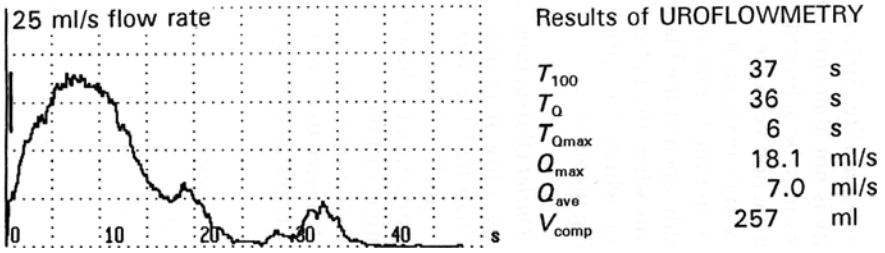

Fig. II.4.31. Uroflowmetry tracing

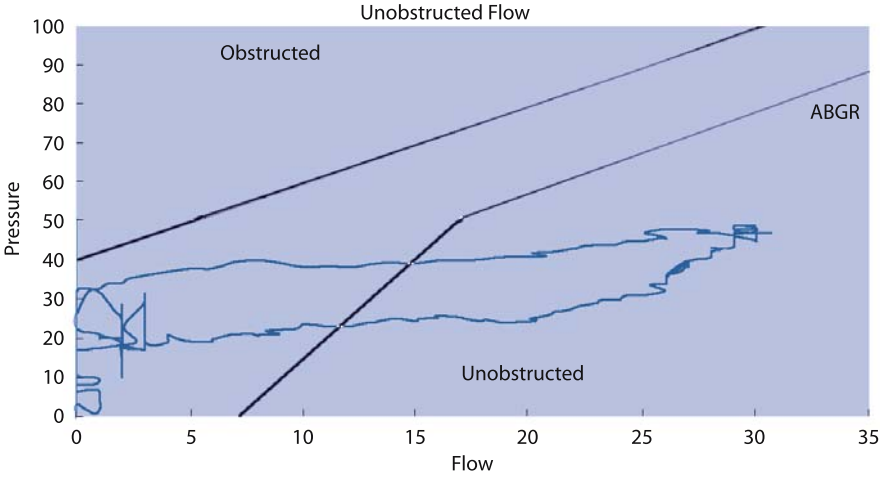

Fig. II.4.32. ICS nomogram

ment is the pressure generated by the contracting bladder muscle at maximum flow corrected for rectal pressure to remove artefact from intra-abdominal pressure. These measurements are then plotted on the ICS nomogram (see Fig. II.4.32), which can then be used to classify the patient as obstructed, unobstructed or equivocal.

II.4.10.1.8 Urethrocystoscopy

Urethrocystoscopy is recommended for men who either have bothersome symptoms and a history of haematuria, bladder cancer, or previous urethral stricture or prior to transurethral resection of the prostate (TURP). It permits direct examination of the lower urinary tract and, when performed under local anaesthesia, can be useful in planning the best invasive (surgical) therapy. Urethral strictures, bladder stones, high bladder neck, diverticulae and other bladder pathologies may be identified and subsequent surgical interventions planned as required. The main side-effects of this procedure are patient discomfort and, infrequently, urinary tract infection, bleeding and urinary retention.

II.4.10.1.9 Transrectal Ultrasound of the Prostate

Transrectal ultrasound examination of the prostate may be used to assess the size and shape of the prostate, which can be important in selecting patients for minimally invasive therapies such as transurethral microwave heat treatments or identifying patients with very large prostates who would be better served by open prostatectomy. Anatomical considerations such as intravesical lobes may impact on the choice of a TURP or incision of prostate. However, the most common indication for transrectal ultrasound of the prostate is as a means of guiding systematic prostate biopsies. These are performed if there are abnormalities on DRE and/or the PSA is elevated. To minimize the risk of sepsis the procedure is covered with oral antibiotics, usually of the quinolone family, to be taken at least an hour prior to biopsy and later that evening. Patients may also experience haemospermia or haematuria for some days or weeks after the biopsy (Desmond et al. 1993).

II.4.10.1.10 Upper Urinary Tract Imaging

Imaging of the upper urinary tract is recommended in the patient with a history of urolithiasis, haematuria, urinary tract infection and renal insufficiency but, because the diagnostic yield is low, it is not used routinely in the assessment of BPH. If imaging is indicated, it has been suggested that ultrasonography and a kidney-ureter-bladder (KUB) plain radiographic film be performed (Hendrikx et al. 1988).

II.4.10.2 Management of BPH

Open prostatectomy and TURP was the widely accepted treatment for BPH before the advent of medical treatments in the 1970s (Caine et al. 1976). Currently TURP is still considered the "gold standard" for the treatment of symptomatic BPH. However, there are now many acceptable alternatives to surgical intervention that are less costly per treatment and have less associated morbidity. As the aim of intervention in the patient with bothersome symptoms from BPH is to improve the quality of life, the lower morbidity of these alternative therapies is a very important factor in patient-driven decisions.

II.4.10.3 Watchful Waiting

Watchful waiting is a policy of careful monitoring for the progression of symptoms and possible complications of BPH but there is no active intervention. Patients should be advised to void completely and to decrease their intake of alcohol- and caffeine-containing beverages late in the day. They should also avoid over-the-counter cold and allergy medication for the reasons stated in the introduction. They are advised to report any changes in symptoms promptly. Patients are usually re-examined annually and the initial evaluation repeated at that time.

II.4.10.4 Pharmacologic Therapy

There are two main classes of medication currently in use for the treatment of symptomatic BPH: these are alpha-adrenergic blockers and 5α-reductase inhibitors. Phytotherapy describes the use of plant extracts and is used widely in some parts of the world. The extract of the American dwarf palm *Serenoa repens* is the most commonly used phytotherapy agent for BPH and the *n*-hexane liposterolic extract of *Serenoa repens*, Permixon (which is manufactured in France), is the product that has been most rigorously investigated to date. A meta-analysis of several open, blind, placebo-controlled and comparative clinical trials of Permixon showed statistically significant improvement in symptoms in men with LUTS compared with placebo and equivalence with finasteride and the alpha-blocker tamsulosin with a lower risk of androgen-dependent unwanted side-effects (Boyle et al. 2004). However, we

will focus our discussion on the commonly prescribed medications for symptomatic BPH.

II.4.10.4.1 Alpha-Adrenergic Blockers

The rationale for alpha-adrenergic blocker use in the treatment of BPH is based on the findings that bladder outlet obstruction (BOO) from BPH is caused by the bulk of the prostate adenoma, the static component, and by the increased prostatic tone mediated by the alpha$_1$-adrenoceptors (α_1AR) in prostatic smooth muscle tissue and bladder neck, termed the dynamic component (Caine 1986). By blocking the alpha-adrenergic receptors at the bladder neck and prostate these medications decrease the prostate tone and decrease the pressure developed in the urethra, which results in diminished BOO (Shapiro et al. 1992).

Phenoxybenzamine is a non-selective alpha-adrenergic blocker which blocks both alpha$_1$ and alpha$_2$-adrenoceptors and was used in initial clinical studies. It was demonstrated that symptoms and urinary flow rate improved but this was associated with significant cardiovascular side-effects in 30 % of patients (Caine et al. 1978). Selective alpha$_1$-adrenoceptor blockers such as prazosin, terazosin, doxazosin and the current uroselective medications alfuzosin and tamsulosin have minimal cardiovascular side-effects.

The American Urological Association has conducted a meta-analysis of alpha-blocker studies which demonstrates that the therapeutic efficacy of all contemporary alpha-blockers appears similar in terms of symptom improvement, quality of life and urinary flow rate (Table II.4.4) (American Urological Association 2003). Alfuzosin and tamsulosin are uroselective and therefore do not require titration of dose and, hence, they are the most widely prescribed in the UK. The alpha-blockers have a quick onset of action with rapid symptom improvement and are associated with a reduction in rates of surgery in developed countries. The most common adverse events associated with alpha-blockers are a 4.4 % incidence of dizziness and postural hypotension (McConnell et al. 2003). However, tamsulosin has found to have a 5 – 10 % incidence of retrograde or delayed ejaculation (Schulman et al. 1999).

II.4.10.4.2 5α-Reductase Inhibition

The rationale for the use of 5α-reductase inhibition (5ARI) is based on the observation that the embryonic development of the prostate depends upon the androgen dihydrotestosterone (DHT) (Peterson et al. 1977). Testosterone is converted to the more potent DHT by the enzyme 5α-reductase. DHT is a powerful ligand for the androgen receptor in the epithelial cells of the prostate and removal or suppression of DHT removes stimulus for cell growth and replication. This has been shown to decrease prostate volume, improve symptom scoring and urinary flow rate and decrease the risk of developing acute urinary retention and BPH-related surgery for both the currently available 5ARIs (Table II.4.5) (Roehrborn et al. 1999; Debruyne et al. 2004). Two 5ARIs are available, finasteride and dutasteride, and they differ in their inhibition of type 1 and type 2 isoenzymes of 5α-reductase. Finasteride is a mono-

Alpha-blockers	AUA/IPSS			Peak flow rate (Q_{max})		
	3 – 9 months	10 – 16 months	> 16 months	3 – 9 months	10 – 16 months	> 16 months
Alfuzosin	–4.44			2.05		
Doxazosin	–5.10	–5.63		3.11	2.98	1.90[a]
Tamsulosin	–4.63	–7.53[a]		1.85	1.86[a]	
Terazosin	–6.22	–5.99		2.51	1.94	2.61[a]

Table II.4.4. Outcome parameters with alpha-blockers: changes in symptom score and peak urinary flow rate

[a] These numbers are based on single-arm analysis – no RCT data available

Table II.4.5. Outcome parameters with 5α-reductase inhibitors (*5ARIs*): changes in symptom score, urinary flow rate, prostate volume and risk of AUR and BPH-related surgery (Marberger et al. 2004)

Study	Patients	Agent	Change in AUA-SI score	Change in peak flow (ml/s)	Change in prostate volume (%)	Reduction in risk of AUR (%)	Reduction in risk of BPH-related surgical intervention (%)
PLESS (McConnell et al. 1998)	3040	Finasteride Placebo	3.3 1.3	+1.9 +0.2	–18 +14	57	55
Dutasteride study (Roehrborn et al. 2002)	4325	Dutasteride Placebo	4.5 2.3	+2.2 +0.6	–25.7 +1.7	57	48

inhibitor of 5AR type 2 whereas dutasteride is a dual inhibitor of both isoenzyme types. The side-effects of the 5ARIs are decreased libido, ejaculatory disorder and impotence affecting 3–5% of patients (Gormley et al. 1992). The results of the Prostate Cancer Prevention Trial demonstrated that long-term use of finasteride is associated with a 25% reduction in the prevalence of prostate cancer but this is balanced by the finding of an increase by a factor of 1.7 in the risk of high-grade tumour among those in whom cancer develops (Thompson et al. 2003a, 2003b).

II.4.10.4.3
Role of Combination Therapy with Alpha$_1$-Blockers and 5α-Reductase Inhibitors

The publication of the 4-year Medical Therapy of Prostatic Symptoms (MTOPS) study, which randomized 3047 men with BPH to treatment with finasteride, doxazosin, a combination of both, or placebo has provided insight into the relative long-term benefits of the two different types of medical therapy alone or in combination. This study confirms that all active treatment arms were associated with significant improvement in symptoms and overall progression. Of the monotherapies, only treatment with 5α-reductase inhibitors demonstrated significant reductions in the risk of acute urinary retention and the progression to invasive therapy. Doxazosin monotherapy resulted in an improvement in symptoms that was significantly greater than with finasteride monotherapy, but inferior to combination therapy. Doxazosin was noted to delay the time to progression of acute urinary retention and the need for invasive therapy but did not significantly reduce the long-term risk of either event. As combination therapy and monotherapy with finasteride were associated with significant reductions in prostate size, whilst there was no observed change in the prostate size in the doxazosin arm, it would appear that 5α-reductase inhibitors alter the natural history of BPH by reducing the size of the prostate (McConnell et al. 2003).

II.4.10.4.4
Summary

BPH is a progressive disease in ageing men and those who are most likely to progress to acute urinary retention or surgery have larger prostates. The aims of treatment of BPH are to alleviate symptoms and prevent progression of the disease. Alpha-blockers have a relatively quick onset of action and should be considered in patients who are symptomatic, whilst only the 5α-reductase inhibitors have been shown to reduce the progression of BPH. Consequently, 5α-reductase inhibitors should be used in combination with alpha-blockers in patients with larger prostate volumes of >30 ml. The 5α-reductase inhibitors have a relatively slow onset of action and the maximum effect is reached at about 6 months. Short-term combination therapy can be useful for patients with enlarged prostates requiring rapid symptom control whereas longer-term combination therapy may benefit patients with severe symptoms with enlarged prostates. The optimum duration of combination therapy may be as short as 6 months.

II.4.10.5
Minimally Invasive Therapies

II.4.10.5.1
Thermal-Based Treatments

Thermal-based treatments use high temperatures to produce coagulation necrosis of prostate tissue. Microwave technology has been used to produce heat but other methods, such as using radiofrequency waves, hot water, high intensity ultrasound and interstitial laser, have been used to similar effect. Thermotherapy refers to a temperature above 45°C and causes tissue necrosis, whereas treatment temperatures of less than 45°C are termed hyperthermia and do not. A multicentre sham-controlled study of technologies using hyperthermia found neither the transurethral nor transrectal treatment to be superior to sham treatments in subjective or objective criteria (Abbou et al. 1995).

Thermotherapy, or transurethral microwave therapy (TUMT), is delivered by the Prostatron. This uses a combination of heat delivered transurethrally and a water balloon to lower prostatic temperature, thereby preventing urethral damage and pain. The efficacy of TUMT has been assessed in several trials though long-term, multicentre studies are lacking (Ahmed et al. 1997; D'Ancona et al. 1997). Whilst it is clear that TUMT is not as effective as TURP in improving the symptom scores and peak flow rate, the improvement in symptoms seems to be related to the energy used. The complications are less than those seen with TURP, with prolonged catheterization and urinary tract infection being the most common. It seems that higher energy devices will be used in the future but continued long-term studies are required to assess this modality of treatment fully.

II.4.10.5.2
Transurethral Needle Ablation

Transurethral needle ablation (TUNA) uses radiofrequency (RF) waves to heat prostatic tissue. The RF energy is delivered into the prostatic tissue via two needles at the tip of the TUNA catheter. A randomized trial comparing TUNA with TURP demonstrated that the symptom improvement was similar to that achieved with TURP but that the improvement in peak urinary

flow rate was not as great. The most commonly reported side-effects were bleeding (32.3%) and urinary tract infection (7.7%). Sexual dysfunction is noted to be rare and there have not been any reported cases of incontinence in any series (Bruskewitz et al. 1998). Again the long-term efficacy of this treatment has not been clearly evaluated as there are no large series with long-term follow-up.

II.4.10.5.3 Laser Treatment

Laser energy can be used to produce coagulation necrosis, vaporization of tissue or resection of tissue. Urologists at present do not agree on the most effective means to deliver laser energy. Some techniques produce tissue coagulation, which causes a delayed sloughing of tissue, whereas other techniques cause immediate vaporization of tissue. Comparisons with TURP have demonstrated that, in the short-term, symptom scores and peak flow rate are equivalent to TURP but the rates of post-operative urinary retention and the need for unplanned catheterization are greater than for TURP. Transurethral holmium laser resection/enucleation is a relatively new technique and it has been demonstrated that, in the hands of an experienced surgeon, the results are comparable to those achieved with open prostatectomy (Kuntz and Lehrich 2002). Long-term data are lacking for these techniques and cost constraints may limit the widespread usage of this technology.

II.4.10.6 Surgical Treatment

II.4.10.6.1 Open Prostatectomy

An open prostatectomy is performed through a lower abdominal incision which is placed either in the midline or transverse suprapubic, and the prostate adenoma is enucleated either through the bladder (transvesical prostatectomy) or through the prostate capsule (Millin's prostatectomy). This procedure is usually performed in patients with very large prostates (>100 g) and data have shown that symptoms improve markedly. The procedure is more invasive and requires a longer hospital stay than TURP.

II.4.10.6.2 Transurethral Resection of the Prostate

TURP is carried out via a resectoscope with a diathermy loop that removes slivers of prostate tissue. The procedure involves a hospital stay of 2–3 days and is performed under general or spinal anaesthesia. The efficacy of this procedure was evaluated definitively in the Veterans Cooperative Study, which demonstrated that 91% of patients had no complications during the first 30 days after surgery, and that the outcomes of surgery were best for patients who were most bothered by their symptoms. Importantly, the study demonstrated there was no difference between the watchful waiting and surgical treatment groups with respect to incontinence and impotence (Wasson et al. 1995). At present, TURP is still considered the "gold standard" against which all invasive procedures are judged.

II.4.10.6.3 Transurethral Incision of the Prostate

Transurethral incision of the prostate is suitable for small prostates with a high bladder neck and no middle lobe enlargement. An incision is made from below the ureteric orifice on both sides and taken through the bladder neck to just proximal to the verumontanum. The results of this procedure are excellent with the incidence of complications being low (Bruskewitz et al. 1998).

II.4.10.7 Complications of Surgical Treatments

II.4.10.7.1 Primary Haemorrhage

This occurs within 24 h of surgery and is related to the surgery itself. There is a need for routine cross-matching, because 5–15% require a blood transfusion after the procedure. Patients who are taking anticoagulants must be identified and steps taken to stop the medication prior to surgery. Warfarin, for example, is usually stopped 5 days preoperatively and anticoagulation covered with heparin. Aspirin should also be stopped 2 weeks prior to surgery.

II.4.10.7.2 Secondary Haemorrhage

This generally happens 10–14 days postoperatively and is a common occurrence. The patient is advised to increase his oral intake of fluid and take appropriate antibiotics as required. Occasionally, the patient may experience a clot retention, in which case urgent catheterization is required.

II.4.10.7.3 Urethral Stricture

This can occur in 3–6% of patients and the most affected sites are the external meatus, the bladder neck and

the bulbar urethra. Urethral strictures usually present 4–5 months after surgery when the patient experiences symptoms of outflow obstruction. Depending on the length and anatomy of the stricture, the treatment may be bouginage or urethotomy to reconstructive surgery of the urethra.

II.4.10.7.4 Retrograde Ejaculation

This is the most common sexual dysfunction after TURP. The incidence is about 70% but only 10% in transurethral incision of the prostate (TUIP). Therefore, patients should be counselled regarding this fact prior to surgery.

II.4.10.8 Therapeutic Options for Prostate Cancer

II.4.10.8.1 Staging of Prostate Cancer

- TRUS and prostate biopsy – allows visual assessment and histological confirmation of prostate cancer
- MRI/CT – assessment of local and metastatic spread
- Isotope bone scan – confirms or excludes skeletal deposits from metastatic prostate cancer
- Pelvic lymph node dissection – most accurate method of assessing metastatic spread to lymph nodes but most clinicians rely on cross-sectional radiological imaging.

II.4.10.8.2 Transrectal Ultrasound and Prostate Biopsy

The early diagnosis of prostate cancer is suspected if there are abnormalities in DRE and/or PSA measurement. Histological confirmation is then sought of the diagnosis by transrectal ultrasound (TRUS) directed biopsies. The procedure should be covered with two doses of oral antibiotics, usually of the quinolone family, to be taken at least an hour prior to biopsy and later that evening. This is to prevent septic complications, which may occur in up to 3% of patients. Patients should also be warned that they may experience haemospermia or haematuria for some days or weeks after the biopsy (Desmond et al. 1993).

II.4.10.8.3 Histological Grading System

The most widely used and recognized grading system for prostate cancer is the Gleason scoring system (Fig. II.4.33). It is based on the low-powered microscopy description of the cancer architecture and this has been correlated with the pathological extent of the disease. Higher Gleason grades (4 or 5), or a Gleason sum grade of greater than 7 has been shown to be predictive of a poor prognosis (Stamey et al. 1999).

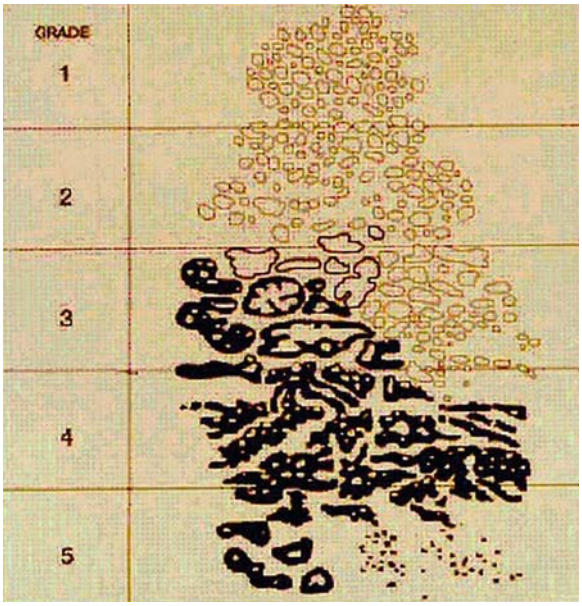

Fig. II.4.33. Gleason Pathological Grading System

II.4.10.8.4 Clinical Staging System

TNM classification for clinical staging of prostate cancer is the most widely used system (see Table II.4.6). It was updated in 2002. The distinction between intracapsular (T1–T2) and extracapsular (T3–T4) disease has a significant impact on treatment decision (Table II.4.6).

II.4.10.8.5 Magnetic Resonance Imaging

Magnetic resonance imaging is now of such a high standard that, with endorectal surface coils, it appears to be the most accurate non-invasive method in detecting locally advanced disease (Fig. II.4.34). It would be appropriate in a selected group of patients when curative treatment is an option and more precise staging will affect the treatment offered.

II.4.10.8.6 Computed Tomography Scanning

Computed tomography (CT) is also useful for assessing local tumour invasion but has the added benefit of

Table II.4.6. Tumour node metastasis (TNM) classification of prostate cancer

Classification	Primary tumour
T	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Clinically unapparent tumour not palpable or visible with imaging
T1a	Tumour an incidental finding at TURP involving 5% or less of resected tissue
T1b	Tumour an incidental finding at TURP in more than 5% of resected tissue
T1c	Tumour identified by needle biopsy
T2	Tumour confined to the prostate
T2a	Tumour involves less than one-half of one lobe
T2b	Tumour involves more than one-half of one lobe
T2c	Tumour involves both lobes
T3	Tumour extends through prostate capsule
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator ani and/or pelvic wall
N	Regional lymph nodes
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M	Distant metastasis
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Non regional lymph node(s)
M1b	Bone(s)
M1c	Other site(s)

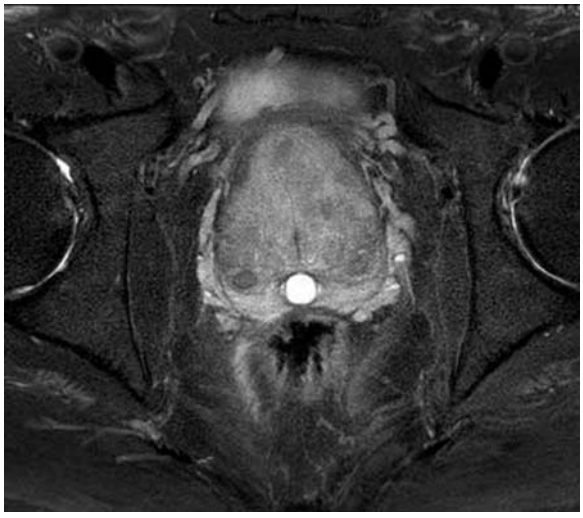

Fig. II.4.34. MRI of prostate

permitting fine needle aspiration of suspected nodal involvement. It is also useful in planning for radiotherapy.

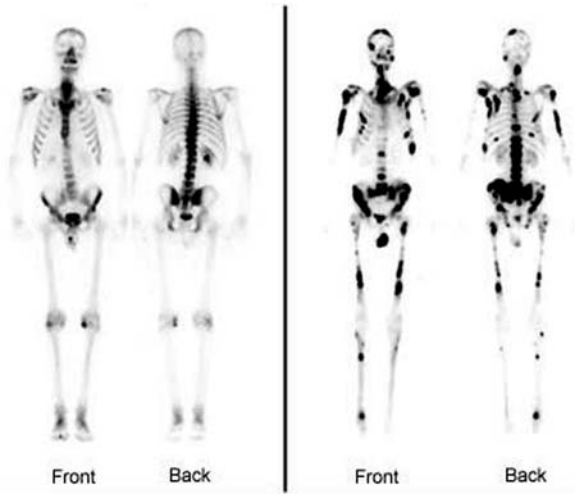

Fig. II.4.35. Normal bone scan on *left*, metastasis demonstrated on *right*

II.4.10.8.7
Bone Isotope Scanning

Bone isotope scanning is the most sensitive method for detecting the presence of bone metastases (Fig. II.4.35). They are seldom positive if the PSA measurement is below 20 ng/ml and almost never when the value is less than 10 ng/ml.

II.4.10.8.8
Pelvic Lymph Node Dissection

Accurate nodal staging is important as the presence of lymph node metastasis precludes curative therapy. Pelvic lymph node dissection remains the most accurate method of assessing nodal metastasis and may be indicated if there is sufficient suspicion of nodal metastasis on imaging, serum PSA > 20 ng/ml and Gleason grade 8 – 10 (Sgrignoli et al. 1994); however, it is more common for surgeons and oncologists to rely on cross-sectional imaging to assess lymph node involvement.

II.4.10.9
Management of Localized Prostate Cancer

II.4.10.9.1
Active Monitoring

Active monitoring describes a treatment strategy of careful monitoring for progression of the disease with postponement of treatment until it is required. This strategy may be appropriate in patients with prostate cancer that is low volume and well differentiated (i.e. Gleason score ≤ 4), especially in patients who have less than 10 years life expectancy and have significant comorbid factors (Kirby 1998). The precise strategy of follow-up for active monitoring varies from centre to

centre. Most would undertake PSA measurement at 3-monthly intervals initially, extending this to 6-monthly assay and then annually in patients with stable PSA. However, active treatment should be considered if serum PSA is rising. Others follow a more aggressive strategy with repeat TRUS-guided prostate biopsies annually (Carter et al. 2002).

II.4.10.9.2 Radical Prostatectomy

Radical prostatectomy is the surgical treatment of prostate cancer and involves the removal of the entire prostate gland and both seminal vesicles. The indications for this treatment are in patients with localized prostate cancer with a life expectancy of more than 10 years. Radical prostatectomy was unpopular as there were concerns of the morbidity associated with the procedure but continence and potency-preserving modifications of the original technique have resulted in decreased complication rates. The retropubic approach is most commonly used as it allows for simultaneous pelvic lymph node assessment to be carried out.

The postoperative complications that patients need to be made aware of are a 7.7% risk of incontinence that persists for more than 1 year, a 9.0% risk of urethral stricture and a 50% risk of erectile dysfunction (Walsh et al. 1994). Patients require to be carefully selected for nerve sparing radical prostatectomy as a higher risk of local recurrence is present if the disease is not truly organ-confined and the surgical margins are positive. If the surgical margins are clear, the postoperative PSA reduces to <0.1 ng/ml. Therefore, any detectable PSA after radical prostatectomy indicates residual or recurrence of cancer and further treatment should be considered, such as radiotherapy or androgen blockade (Huland et al. 1994). Long-term studies have demonstrated the 15-year cancer-specific survival rate of 90% (Han et al. 2001).

II.4.10.9.3 External Beam Radiation Therapy

External beam radiation therapy, for patients with localized prostate cancer, has been shown to produce treatment results that are comparable to results achieved with radical prostatectomy. The long-term disease-free survival rate is 70–90% (Zietman et al. 1995; Hahn et al. 1996). The adverse side-effects associated with this treatment are urinary frequency due to radiation cystitis, bowel upset due to radiation proctitis and the risk of erectile dysfunction.

II.4.10.9.4 External Beam Radiation Therapy and Adjuvant Hormonal Therapy

Adjuvant hormonal ablation therapy with LHRHa prior to and during external beam radiation has been shown to offer better outcomes than radiotherapy alone (Bolla 1999). The clinical disease-free survival rate was improved from 40% to 75%. The study noted that hot flushes occurred in 33% of the combined therapy group compared to the radiotherapy group. Consequently, most patients undergoing external radiotherapy for prostate cancer now receive adjuvant hormone ablation.

II.4.10.9.5 Three-Dimensional Conformal Radiation Therapy

Three-dimensional conformal radiation therapy (3D-CRT) allows more accurate targeting of radiation at cancer tissues, thereby increasing the radiation dose to these sites and sparing normal tissue. This then lowers the toxicity and morbidity of the treatment. Studies have demonstrated up to 90% biochemical freedom from failure (i.e. PSA <0.1 ng/ml) for 5 years (Anderson et al. 1998).

II.4.10.9.6 Interstitial Radiotherapy or Brachytherapy

Interstitial radiotherapy describes the technique of placing a radioactive source within the prostate, allowing the delivery of a high dose of radiation to the prostate and sparing surrounding tissues.

High dose rate (HDR) interstitial radiotherapy involves an operation for the placement of needles within the prostate and short-term results have demonstrated comparable results to those of surgery and external beam radiotherapy (Khan et al. 1992). The incidence of side-effects such as proctitis seems to be higher and this may be suitable for patients with advanced rather than localized disease.

Low dose rate (LDR) interstitial therapy can be administered in an outpatient setting and involves placement of radioactive sources within the prostate under ultrasound guidance. The long-term side-effect profile is better than that of HDR therapy with <1–2% reporting incontinence and 1–2% of patients reporting proctitis (Blasko et al. 1996). Results have indicated that at 9 years the biochemical control rate was 83.5% in localized prostate cancer (Blasko et al. 2000).

II.4.10.9.7 Neoadjuvant Therapy Prior to Curative Treatment

This describes therapy given prior to definitive treatment with the modalities outlined above. As prostate

cancer is an androgen-dependent tumour, neoadjuvant hormone treatment is an attractive prospect. It has been shown in vitro that prostate cancer cells undergo apoptosis, or cell death, when androgens are withdrawn (Kyprianou et al. 1990).

II.4.10.9.8 Neoadjuvant Therapy Prior to Surgery

In a number of studies, it was demonstrated that there was a significantly lower number of positive surgical margins in patients treated with neoadjuvant therapy (NAT). Unfortunately, follow-up results did not demonstrate a reduced PSA failure rate. When considering surgical technique, it was noted that surgery was slightly more difficult in patients who had received LHRHa prior to surgery (Soloway et al. 1995).

II.4.10.9.9 Neoadjuvant Therapy Prior to Radiotherapy

The current studies regarding NAT prior to radiotherapy have demonstrated that, in the initial 5 years of follow-up, the NHT group had improved local control and disease progression rates but, unfortunately, an update could not demonstrate improved overall survival (Pilepich et al. 1995).

II.4.10.10 Management of Locally Advanced Prostate Cancer and Metastatic Disease

Hormonal therapy is indicated in patients with locally advanced prostate cancer. Hormonal therapy describes any treatment that reduces the level of testosterone. Huggins and Hodges (1941) demonstrated the androgen dependence of prostate cancer. Whilst hormone-based therapy does not cure prostate cancer, it can diminish the size of the cancer and slow the growth and spread of metastasis. It is now generally agreed that prompt intervention with hormone therapy as soon as locally advanced or metastatic disease is diagnosed will be beneficial in terms of overall survival, but this must be balanced against the side-effects of these therapies (The Medical Research Council Prostate Cancer Working Party Investigators Group 1997). As with all forms of treatment for prostate cancer the response to treatment with hormone manipulation may be assessed and monitored by assay of serial serum PSA levels.

II.4.10.10.1 Surgical Castration

Bilateral orchiectomy is the gold standard against which all other hormone treatments must be compared. The surgical procedure is well tolerated by patients and can be performed under a short general anaesthetic or local anaesthesia. About 80% of patients have an excellent response to this mode of treatment with a mean duration of effectiveness of 2.5 years. The disadvantages of this treatment are the psychological effect of losing the testes and surgical morbidity. The main side-effects of testosterone suppression, whether surgical or chemically induced, are erectile dysfunction, hot flushes and occasionally breast tenderness.

II.4.10.10.2 Oestrogens

Oestrogens reduce the level of testosterone by acting on the negative feedback mechanism in the pituitary-gonadal axis. It blocks the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). The most commonly used oestrogen is diethylstilboestrol (DES), but used at a dose of 5 mg/day, this produces significant cardiovascular toxicity. This risk is reduced with doses of 1 mg/day, particularly when low-dose aspirin is prescribed in conjunction, but serum testosterone levels do not fall to the levels seen in castrated patients (Shearer et al. 1973; Garnick 1986). As yet, further studies are required to elucidate the role of oestrogens in the treatment of prostate cancer (Iversen 1998).

II.4.10.10.3 LHRH Analogues

Luteinizing hormone releasing hormone analogues (LHRHa) such as leuprolide, buserelin and goserelin have been shown to be as effective as surgical castration in suppressing serum testosterone and do not increase the risk of cardiovascular toxicity. LHRHa are chemically similar to oestrogens and interfere with the negative feedback mechanism of the pituitary–gonadal axis. However, they also cause an initial rise in LH and FSH release from the pituitary and thereby testosterone production increases. This is described as the "flare phenomenon" as this can cause an increase in prostate tumour growth. Therefore, 4 weeks of adjuvant treatment with an anti-androgen such as bicalutamide (50 mg once daily), starting 1 week prior to the first injection of LHRHa, is recommended to prevent deleterious consequences of tumour flare associated with the brief rise in testosterone levels. LHRHa are given as a monthly or 3-monthly subcutaneous depot injection. The major side-effects of hormone treatment are loss of

libido and impotence. Hot flushes and gynaecomastia occur to varying degrees.

II.4.10.10.4 Anti-Androgens

Anti-androgens are a group of compounds that inhibit the action of androgens at the cellular level. They may be used in conjunction with LHRHa to achieve what is known as "maximal androgen blockade", which is discussed later. Anti-androgens are classified according to their chemical structure with cyproterone acetate as a steroidal anti-androgen and nilutamide, flutamide and bicalutamide as non-steroidal anti-androgens. All of these compounds compete for androgen receptors but steroidal anti-androgens also lower LH and testosterone levels, which may lead to impotence and loss of libido. The non-steroidal anti-androgens, on the other hand, tend to increase serum testosterone due to increased gonadotrophin secretion (Soloway and Matzkin 1993).

II.4.10.10.5 Non-Steroidal Anti-Androgens

Nilutamide is not recommended for monotherapy and currently there is no evidence to support its use in this context. Flutamide has been used as monotherapy for metastatic prostate cancer but currently its use is recommended only in combination with either surgical or medical castration (Decensi et al. 1991). Bicalutamide has been compared with surgical and medical castration in several studies and has been found to be less effective in terms of time to progression and median survival (Bales and Chodak 1996). The role of bicalutamide as monotherapy is currently being investigated in the largest clinical trial in prostate cancer to date. The Bicalutamide Early Prostate Cancer Programme has not matured yet but will provide invaluable insight into the effect of early hormonal treatment on survival (See et al. 2001, 2002). A common side-effect of bicalutamide therapy is the occurrence of bothersome gynaecomastia, requiring complementary treatment with local radiotherapy, medical treatment (anti-oestrogens, e.g. tamoxifen) or surgery (Iversen et al. 2000).

II.4.10.10.6 Steroidal Anti-Androgens

Cyproterone acetate is a potent steroidal anti-androgen and causes suppression of testosterone and LH secretion. This has been evaluated in a number of earlier studies showing that, compared to treatment with DES, there was no difference with respect to cancer progression or overall survival (Pavone-Macaluso et al. 1986). The side-effect profiles of this treatment are loss of libido and potency. Abnormal liver function tests have been observed with long-term use (Schroder et al. 2000).

II.4.10.10.7 Maximal Androgen Blockade

Maximal androgen blockade (MAB) or total androgen suppression is the simultaneous suppression/blockade of both testicular and adrenal androgens as first-line treatment. This modality of treatment has been studied extensively and results from the majority of studies demonstrate that the 5-year survival with MAB amounted to 25.4% versus 23.4% with castration or LHRHa therapy; this difference did not reach statistical significance (Prostate Cancer Trialist' Collaborative Group 2000). The studies, however, demonstrate that patients receiving MAB achieved a quicker response to clinical symptoms and markers. Therefore, there may be an indication for MAB in patients who have severe symptoms due to local cancer spread or metastasis and very high PSA and alkaline phosphatase.

II.4.10.11 Treatment of Hormone Relapsed Prostate Cancer

Hormone relapsed prostate cancer is defined as cancer that returns after initial hormone therapy. There are many different terms for this, such as hormone-resistant or refractory prostate cancer, androgen- or hormone-independent prostate cancer. Analysis of the many studies examining the outcomes of treatment for hormone relapsed prostate cancer demonstrate that the mean time to progression ranges from 12 to 18 months and the mean time for survival ranges from 2 to 3 years (Eisenberger et al. 1986, 1998; Denis et al. 1993).

II.4.10.11.1 Anti-Androgen Withdrawal

It has been noted that withdrawal of anti-androgen can result in improved clinical symptoms and a decrease in PSA (Scher and Kelly 1993). This was initially seen with flutamide therapy and has been reported with bicalutamide therapy (Small and Carroll 1994). Therefore, in patients treated with anti-androgens who are diagnosed with hormone relapsed prostate cancer by serial rises in their serum PSA, the initial step should be to consider discontinuing therapy and to monitor PSA levels closely before considering the next treatment option.

II.4.10.11.2 Second-Line Hormonal Therapy

Several studies have examined this treatment modality and have concluded that the median duration of response ranged between 2 and 4 months. The compounds used have been diethylstilbestrol (DES), ketoconazole and corticosteroids (Storlie et al. 1995).

II.4.10.11.3 Cytotoxic Chemotherapy

Chemotherapy can be given more safely and is better tolerated now that supportive care has been improved with the use of haematological growth factors and anti-emetics. Several combinations of chemotherapy agents have been assessed and there has been an encouraging initial result. A study in 1995 demonstrated that treatment with mitoxantrone (related to anthracycline) combined with prednisolone resulted in a significant improvement in quality of life issues (Tannock et al. 1996). Treatment with estramustine in combination with different compounds has also been studied and results have been promising. Cyclophosphamide is an alkylating agent and it has been found that an oral preparation of this agent is less toxic than intravenous treatment and seems to have greater efficacy (Maulard-Durdux et al. 1996). Recent data regarding treatment with docetaxel and prednisolone have shown an improvement in survival compared to mitoxantrone and prednisolone therapy (Tannock et al. 2004).

II.4.10.11.4 Palliative Management of Bone Pain and Spinal Cord Compression

Metastatic prostate cancer frequently involves bone and one of the most common clinical problems is bone pain. The focal area should be assessed with plain radiographs and possibly a bone scan to rule out pathological fractures, especially in weight-bearing bones. Localized radiotherapy has been shown to control focal bone pain. If the deposits are diffuse, then intravenous strontium-89 can improve symptoms (Laing et al. 1991). A study demonstrated that zoledronic acid, a bisphosphonate, has clinical benefit in patients with advanced disease. It was shown that there was a reduction in bone pain and a delay of onset of skeletal complications (Saad et al. 2002). Growth of metastatic bone deposits may also cause spinal cord compression or interfere with haematological function if the bone marrow is replaced with cancerous tissue. The incidence of spinal cord compression is quite high and early recognition and treatment is required to avoid the serious sequelae of loss of sphincter control of the bladder and bowel or complete paraplegia. Emergency treatment involves high-dose corticosteroids, external beam radiotherapy and possible surgical decompression (Sorensen et al. 1990). Percutaneous vertebroplasty is a minimally invasive technique whereby acrylate cement is injected into the compressed vertebra to relieve pain and to provide strength (Weill et al. 1996). There is considerable experience in continental Europe but limited experience in the United Kingdom in this technique (Hide and Gangi 2004).

II.4.10.11.5 The Future

The management of hormone relapsed prostate cancer remains a challenge for clinicians due to the fact that no second-line therapy has been found to be as efficacious as androgen ablation has been for first-line treatment. Currently, important advances are being made in the fields of molecular and cell biology of prostate cancer and new drugs are being developed, which will increase our understanding of hormone relapsed prostate cancer and help improve care for these patients.

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